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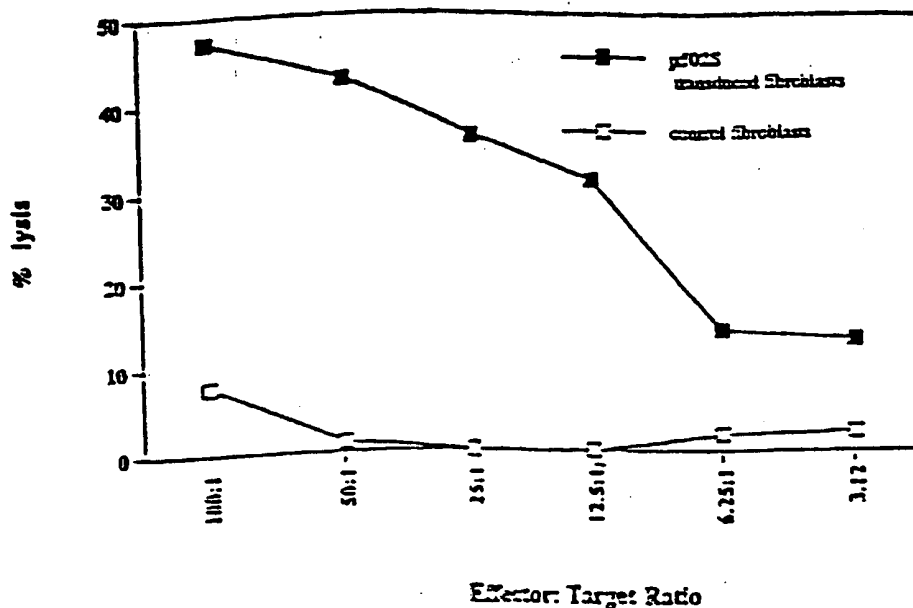
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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER



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(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.



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## COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

### 5 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides  
10 are useful in pharmaceutical compositions, e.g., vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

### BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although Cancer is a significant health problem throughout the world. Although advances have  
15 been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with  
20 an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

25 In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

## 10 SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,



381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

5 (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

10 (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

15 (g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

20 In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

25 The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences  
30 recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or  
5 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the  
10 fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-  
15 629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626,  
20 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic  
30 applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to  
5 a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative  
10 antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

15 The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic  
20 polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human  
25 patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for  
30 inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for  
5 removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the  
10 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a  
15 polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for  
20 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide  
25 comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release

bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16  
SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1  
SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9  
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4  
5 SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17  
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17  
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12  
SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12  
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862  
10 SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862  
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13  
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13  
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19  
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19  
15 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25  
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25  
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24  
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24  
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58  
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SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63  
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63  
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4  
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4  
25 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14  
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14  
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12  
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16  
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21  
30 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48



SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55

SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2

SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6

SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858

5 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860

SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861

SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864

SEQ ID NO: 41 is the determined cDNA sequence for P5

SEQ ID NO: 42 is the determined cDNA sequence for P8

10 SEQ ID NO: 43 is the determined cDNA sequence for P9

SEQ ID NO: 44 is the determined cDNA sequence for P18

SEQ ID NO: 45 is the determined cDNA sequence for P20

SEQ ID NO: 46 is the determined cDNA sequence for P29

SEQ ID NO: 47 is the determined cDNA sequence for P30

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SEQ ID NO: 49 is the determined cDNA sequence for P36

SEQ ID NO: 50 is the determined cDNA sequence for P38

SEQ ID NO: 51 is the determined cDNA sequence for P39

SEQ ID NO: 52 is the determined cDNA sequence for P42

20 SEQ ID NO: 53 is the determined cDNA sequence for P47

SEQ ID NO: 54 is the determined cDNA sequence for P49

SEQ ID NO: 55 is the determined cDNA sequence for P50

SEQ ID NO: 56 is the determined cDNA sequence for P53

SEQ ID NO: 57 is the determined cDNA sequence for P55

25 SEQ ID NO: 58 is the determined cDNA sequence for P60

SEQ ID NO: 59 is the determined cDNA sequence for P64

SEQ ID NO: 60 is the determined cDNA sequence for P65

SEQ ID NO: 61 is the determined cDNA sequence for P73

SEQ ID NO: 62 is the determined cDNA sequence for P75

30 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79

SEQ ID NO: 65 is the determined cDNA sequence for P84

SEQ ID NO: 66 is the determined cDNA sequence for P68

SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred

5 to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82

SEQ ID NO: 69 is the determined cDNA sequence for U1-3064

SEQ ID NO: 70 is the determined cDNA sequence for U1-3065

SEQ ID NO: 71 is the determined cDNA sequence for V1-3692

10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905

SEQ ID NO: 73 is the determined cDNA sequence for V1-3686

SEQ ID NO: 74 is the determined cDNA sequence for R1-2330

SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976

SEQ ID NO: 76 is the determined cDNA sequence for V1-3679

15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736

SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738

SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741

SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744

SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734

20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774

SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781

SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785

SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787

SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796

25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807

SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810

SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811

SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876

SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884

30 SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761
- SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762
- SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766
- SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770
- 5 SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771
- SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772
- SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297
- SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309
- SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278
- 10 SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288
- SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283
- SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304
- SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296
- SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280
- 15 SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12  
(also referred to as P504S)
- SEQ ID NO: 108 is the predicted amino acid sequence for F1-12
- SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17
- SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12
- 20 (also referred to as P501S)
- SEQ ID NO: 111 is the determined full length cDNA sequence for N1-  
1862 (also referred to as P503S)
- SEQ ID NO: 112 is the predicted amino acid sequence for J1-17
- SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also  
25 referred to as P501S)
- SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also  
referred to as P503S)
- SEQ ID NO: 115 is the determined cDNA sequence for P89
- SEQ ID NO: 116 is the determined cDNA sequence for P90
- 30 SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95  
SEQ ID NO: 119 is the determined cDNA sequence for P98  
SEQ ID NO: 120 is the determined cDNA sequence for P102  
SEQ ID NO: 121 is the determined cDNA sequence for P110  
5 SEQ ID NO: 122 is the determined cDNA sequence for P111  
SEQ ID NO: 123 is the determined cDNA sequence for P114  
SEQ ID NO: 124 is the determined cDNA sequence for P115  
SEQ ID NO: 125 is the determined cDNA sequence for P116  
SEQ ID NO: 126 is the determined cDNA sequence for P124  
10 SEQ ID NO: 127 is the determined cDNA sequence for P126  
SEQ ID NO: 128 is the determined cDNA sequence for P130  
SEQ ID NO: 129 is the determined cDNA sequence for P133  
SEQ ID NO: 130 is the determined cDNA sequence for P138  
SEQ ID NO: 131 is the determined cDNA sequence for P143  
15 SEQ ID NO: 132 is the determined cDNA sequence for P151  
SEQ ID NO: 133 is the determined cDNA sequence for P156  
SEQ ID NO: 134 is the determined cDNA sequence for P157  
SEQ ID NO: 135 is the determined cDNA sequence for P166  
SEQ ID NO: 136 is the determined cDNA sequence for P176  
20 SEQ ID NO: 137 is the determined cDNA sequence for P178  
SEQ ID NO: 138 is the determined cDNA sequence for P179  
SEQ ID NO: 139 is the determined cDNA sequence for P185  
SEQ ID NO: 140 is the determined cDNA sequence for P192  
SEQ ID NO: 141 is the determined cDNA sequence for P201  
25 SEQ ID NO: 142 is the determined cDNA sequence for P204  
SEQ ID NO: 143 is the determined cDNA sequence for P208  
SEQ ID NO: 144 is the determined cDNA sequence for P211  
SEQ ID NO: 145 is the determined cDNA sequence for P213  
SEQ ID NO: 146 is the determined cDNA sequence for P219  
30 SEQ ID NO: 147 is the determined cDNA sequence for P237

SEQ ID NO: 148 is the determined cDNA sequence for P239  
SEQ ID NO: 149 is the determined cDNA sequence for P248  
SEQ ID NO: 150 is the determined cDNA sequence for P251  
SEQ ID NO: 151 is the determined cDNA sequence for P255  
5 SEQ ID NO: 152 is the determined cDNA sequence for P256  
SEQ ID NO: 153 is the determined cDNA sequence for P259  
SEQ ID NO: 154 is the determined cDNA sequence for P260  
SEQ ID NO: 155 is the determined cDNA sequence for P263  
SEQ ID NO: 156 is the determined cDNA sequence for P264  
10 SEQ ID NO: 157 is the determined cDNA sequence for P266  
SEQ ID NO: 158 is the determined cDNA sequence for P270  
SEQ ID NO: 159 is the determined cDNA sequence for P272  
SEQ ID NO: 160 is the determined cDNA sequence for P278  
SEQ ID NO: 161 is the determined cDNA sequence for P105  
15 SEQ ID NO: 162 is the determined cDNA sequence for P107  
SEQ ID NO: 163 is the determined cDNA sequence for P137  
SEQ ID NO: 164 is the determined cDNA sequence for P194  
SEQ ID NO: 165 is the determined cDNA sequence for P195  
SEQ ID NO: 166 is the determined cDNA sequence for P196  
20 SEQ ID NO: 167 is the determined cDNA sequence for P220  
SEQ ID NO: 168 is the determined cDNA sequence for P234  
SEQ ID NO: 169 is the determined cDNA sequence for P235  
SEQ ID NO: 170 is the determined cDNA sequence for P243  
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1  
25 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1  
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2  
SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6  
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13  
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13  
30 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14

SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-

4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-

5 4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-

4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-

4744

10

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-

4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-

4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-

15 4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-

4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-

4796

20

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-

4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-

25 4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-

4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-

4896

- 4761 SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-
- 4762 SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-
- 5 4766 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-
- SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770
- SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771
- SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-
- 10 4772
- SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-
- 4309
- SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-
- 4278
- 15 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-
- 4288
- SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-
- 4283
- SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-
- 20 4304
- SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-
- 4296
- SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-
- 4280
- 25 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd
- SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con
- SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev
- SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd
- SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev
- 30 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

5 SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev  
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd  
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev  
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd  
SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev  
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd  
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev  
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev  
10 SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd  
SEQ ID NO: 222 is the determined cDNA sequence for g-βrev  
SEQ ID NO: 223 is the determined cDNA sequence for P509S  
SEQ ID NO: 224 is the determined cDNA sequence for P510S  
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5  
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11  
15 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6  
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7  
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13  
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14  
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23  
20 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24  
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25  
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30  
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34  
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35  
25 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36  
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38  
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39  
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40  
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41  
30 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42



SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45  
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46  
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51  
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56  
5 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64  
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65  
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67  
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76  
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84  
10 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85  
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86  
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87  
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88  
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1  
15 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2  
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2  
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1  
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2  
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3  
20 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4  
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5  
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6  
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6  
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5  
25 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6  
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8  
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7  
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9  
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10  
30 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

5 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12  
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12  
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11  
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11  
SEQ ID NO: 277 is the determined cDNA sequence for JP1C12  
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12  
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12  
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2  
10 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1  
SEQ ID NO: 282 is the determined cDNA sequence for JP8H2  
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3  
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4  
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3  
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4  
15 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6  
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6  
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5  
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8  
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7  
20 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7  
SEQ ID NO: 293 is the determined cDNA sequence for P8D8  
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7  
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8  
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8  
25 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10  
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10  
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9  
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10  
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9  
30 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

SEQ ID NO: 303 is the determined cDNA sequence for JP8C12  
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11  
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12  
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12  
5 SEQ ID NO: 307 is the determined cDNA sequence for P711P  
SEQ ID NO: 308 is the determined cDNA sequence for P712P  
SEQ ID NO: 309 is the determined cDNA sequence for CLONE23  
SEQ ID NO: 310 is the determined cDNA sequence for P774P  
SEQ ID NO: 311 is the determined cDNA sequence for P775P  
10 SEQ ID NO: 312 is the determined cDNA sequence for P715P  
SEQ ID NO: 313 is the determined cDNA sequence for P710P  
SEQ ID NO: 314 is the determined cDNA sequence for P767P  
SEQ ID NO: 315 is the determined cDNA sequence for P768P  
SEQ ID NO: 316-325 are the determined cDNA sequences of previously

15 isolated genes

SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5  
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5  
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26  
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26  
20 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23  
SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23  
SEQ ID NO: 332 is the determined full length cDNA sequence for

P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P  
25 (also referred to as 11-C9)

SEQ ID NO: 334 is the determined cDNA sequence for P714P

SEQ ID NO: 335 is the determined cDNA sequence for P705P (also  
referred to as 9-F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

30 SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEQ ID NO: 339 is the predicted amino acid sequence of P509S

SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

5 SEQ ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

10 SEQ ID NO: 345 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing  
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase  
(SHMT)

15 SEQ ID NO: 347 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens natural resistance-associated macrophage protein2  
(NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)

20 SEQ ID NO: 349 is the determined cDNA sequence for a clone showing  
homology to Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

25 SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

30 SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P.

SEQ ID NO: 362 is the determined cDNA sequence for P788P

5      SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice  
variants of B305D.

10      SEQ ID NO: 376 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 372.

15      SEQ ID NO: 378 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 375.

20      SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for  
P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

25      SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO: 386 is the cDNA sequence for 23320.

SEQ ID NO: 387 is the cDNA sequence for CGI-69.

SEQ ID NO: 388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO: 389 is the cDNA sequence for 23379.

30      SEQ ID NO: 390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

5 SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor

PDEF.

10 SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

15 SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as

P1020C).

20 SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

25 SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

30 SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.  
SEQ ID NO:420 is the cDNA sequence for 22581.  
SEQ ID NO:421 is the cDNA sequence for 22582.  
SEQ ID NO:422 is the cDNA sequence for 22583.  
5 SEQ ID NO:423 is the cDNA sequence for 22584.  
SEQ ID NO:424 is the cDNA sequence for 22585.  
SEQ ID NO:425 is the cDNA sequence for 22586.  
SEQ ID NO:426 is the cDNA sequence for 22587.  
SEQ ID NO:427 is the cDNA sequence for 22588.  
10 SEQ ID NO:428 is the cDNA sequence for 22589.  
SEQ ID NO:429 is the cDNA sequence for 22590.  
SEQ ID NO:430 is the cDNA sequence for 22591.  
SEQ ID NO:431 is the cDNA sequence for 22592.  
SEQ ID NO:432 is the cDNA sequence for 22593.  
15 SEQ ID NO:433 is the cDNA sequence for 22594.  
SEQ ID NO:434 is the cDNA sequence for 22595.  
SEQ ID NO:435 is the cDNA sequence for 22596.  
SEQ ID NO:436 is the cDNA sequence for 22847.  
SEQ ID NO:437 is the cDNA sequence for 22848.  
20 SEQ ID NO:438 is the cDNA sequence for 22849.  
SEQ ID NO:439 is the cDNA sequence for 22851.  
SEQ ID NO:440 is the cDNA sequence for 22852.  
SEQ ID NO:441 is the cDNA sequence for 22853.  
SEQ ID NO:442 is the cDNA sequence for 22854.  
25 SEQ ID NO:443 is the cDNA sequence for 22855.  
SEQ ID NO:444 is the cDNA sequence for 22856.  
SEQ ID NO:445 is the cDNA sequence for 22857.  
SEQ ID NO:446 is the cDNA sequence for 23601.  
SEQ ID NO:447 is the cDNA sequence for 23602.  
30 SEQ ID NO:448 is the cDNA sequence for 23605.

SEQ ID NO:449 is the cDNA sequence for 23606.

SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

5 SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

10 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for clone 23054.

SEQ ID NO:462-467 are cDNA sequences for known genes.

15 SEQ ID NO:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO: 473 is the determined cDNA sequence for a first splice variant of P775P (referred to as 27505).

20 SEQ ID NO: 474 is the determined cDNA sequence for a second splice variant of P775P (referred to as 19947).

SEQ ID NO: 475 is the determined cDNA sequence for a third splice variant of P775P (referred to as 19941).

SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice variant of P775P (referred to as 19937).

25 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

SEQ ID NO: 478 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 474.

30 SEQ ID NO: 479 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 475.



SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

5           SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

10           SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

15           SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

20           SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

25           SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

30           SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ

ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

5 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID

NO: 366.

SEQ ID NO: 531 is the cDNA sequence of the open reading frame of

10 SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of

SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ

15 ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ

ID NO: 535.

20 SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ

ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

25 SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by  
predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

30 of P776P referred to as contig 6.  
SEQ ID NO: 570 is the determined cDNA sequence for a splice variant

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

5        SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

10       SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

15       SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

20       SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

25       SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

30       SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

5                   SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P  
and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and  
PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

10                   SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of  
P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-14.

15                   SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-10.

20                   SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO:  
626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO:  
623.

25                   SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID  
NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-  
specific transglutaminase gene (also referred to herein as P558S).

30                   SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-  
specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of  
SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of  
SEQ ID NO: 631.

5 SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO:  
634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic  
variant of P788P.

10 SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO:  
636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from  
P703P.

15 SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of  
P703P.

SEQ ID NO: 672 and 673 are PCR primers.

20 SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion  
of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of  
P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis*  
antigen Ra12.

25 SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C  
construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

5 SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

10 SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

15 SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

20 SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

25 SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

5 SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

10 SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

15 SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

20 SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

25 SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

30 SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2,

5           SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

10           SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

15           SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

20           SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

25           SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

30           SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.



SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

5 SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

10 SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an  $\alpha$  prepro-P501S recombinant protein.

## 15 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such  
20 polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.*, T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of  
25 the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether  
5 supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

#### Polypeptide Compositions

10 As used herein, the term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-  
15 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic  
20 determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382  
25 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention  
5 comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

10 The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present  
15 invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other  
20 normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are  
25 immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory*  
30 *Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example,  $^{125}\text{I}$ -labeled Protein A.

5           As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.

10   Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they

15   specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that

20   is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that

25   have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain

30   has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a  
5 polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies  
10 that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments  
15 comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568,  
20 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591,  
25 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%,  
30 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or  
5 T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth  
10 herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of  
15 the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants  
20 include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide  
25 chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is  
30 desired to alter the amino acid sequence of a polypeptide to create an equivalent, or

even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its



hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5);  
5 glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are  
10 within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of  
15 its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0  $\pm$  1); glutamate (+3.0  $\pm$  1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5  $\pm$  1); alanine (−0.5); histidine (−0.5); cysteine  
20 (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$   
25 is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that  
30 take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of  
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values  
15 include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a  
20 preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For  
30 example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 10 Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 15 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

25 Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al.,

*Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to  
5 separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and  
10 transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus,  
15 tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression  
20 and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent  
25 and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also*, Skeiky et al., *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the  
30 purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous

immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been  
5 exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at  
10 residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention,  
15 when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4<sup>+</sup> T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further  
20 described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a  
25 growing amino acid chain. *See Merrifield, J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of  
30 the invention are isolated. An "isolated" polypeptide is one that is removed from its



original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99%  
5 pure.

#### Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total  
10 genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude  
15 genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may  
20 be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-  
25 to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

5 Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655,  
10 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722,  
15 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765,  
20 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-  
25 335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a  
30 polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable  
5 highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides  
10 that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

15 The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment  
20 of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated  
25 to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison  
30 window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 5                   Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 10 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,
- 15 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be

20 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these

25 algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402

30 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides

that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions  
5 and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of  
10 immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more  
15 nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on  
20 both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors  
25 contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA  
30 molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single  
5 stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

10 In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded  
15 vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected  
20 which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be  
25 obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.



As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable  
5 signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known  
10 rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

15 In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

20 In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence  
25 disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a  
30 sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of  
5 contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in  
10 various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger  
15 contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in  
20 length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

25 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure,  $T_m$ , binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement  
5 that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,  
10 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to  
15 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many  
20 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of  
25 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action  
30 (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the

specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis  $\delta$  virus, group I intron or RNaseP RNA (in association with an RNA  
5 guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic  
Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the  
10 hepatitis  $\delta$  virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada  
*et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and  
Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive,  
15 Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid  
molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have  
nucleotide sequences within or surrounding that substrate binding site which impart an  
20 RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically  
incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as  
25 described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that  
30 prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes



expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem.* 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

#### Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., *Taq* polymerase). If the target sequence is present  
5 in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse  
10 transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR™ amplification technique, are readily known and available in  
15 the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat.  
20 Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded  
25 RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara,  
30 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification.

5 Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with  $^{32}\text{P}$ ) using well known techniques. A bacterial or  
10 bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may  
15 be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can  
20 then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., *Nucl. Acids Res.*  
25 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a  
30 known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic.* 1:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res.* 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

10 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be  
15 engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be  
25 achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable  
30 techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5 In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing  
10 sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York.  
15 N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,  
20 or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

25 The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription  
30 and translation elements, including constitutive and inducible promoters, may be used.



For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of  $\beta$ -galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

5           A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal  
10 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; *Serological Methods, a Laboratory Manual*, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

15           A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions  
20 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used  
25 include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

          Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained  
30 intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMLAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant  
5 or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

10 Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant ( $K_d$ ) of the interaction, wherein a smaller  $K_d$  represents a greater  
15 affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both  
20 the "on rate constant" ( $K_{on}$ ) and the "off rate constant" ( $K_{off}$ ) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of  $K_{off}/K_{on}$  enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant  $K_d$ . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

25 An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable  
30 regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation



of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')<sub>2</sub>" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V<sub>H</sub>::V<sub>L</sub> heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V<sub>H</sub>::V<sub>L</sub> heterodimer which is expressed from a gene fusion including V<sub>H</sub>- and V<sub>L</sub>-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) *Nature* 349:293-299; Lobuglio et al. (1989) *Proc. Nat. Acad. Sci. USA* 86:4220-4224; Shaw et al. (1987) *J Immunol.* 138:4534-4538; and Brown et al. (1987) *Cancer Res.* 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Kiechmann et al. (1988) *Nature* 332:323-327; Verhoeyen et al. (1988) *Science* 239:1534-1536; and Jones et al. (1986) *Nature* 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) *Ann. Rev. Biochem.* 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred  
5 toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a  
10 substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an  
15 antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which  
20 otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups,  
25 sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of  
30 different cleavable linker groups have been described. The mechanisms for the

intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by  
5 serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.  
10 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent  
15 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for  
20 radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For  
25 example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

#### T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et



al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines 90* (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129;

Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK<sup>sup</sup>(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, e.g., WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression  
5 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable  
10 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)  
15 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,  
20 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639  
25 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances  
30 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous

antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.

5 Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated  
10 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition  
15 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN- $\gamma$ , TNF $\alpha$ , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as  
20 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,  
25 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL<sup>®</sup> adjuvants are available from Corixa Corporation (Seattle, WA; see, for example, US  
30 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by

5 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example

10 combinations of at least two of the following group comprising QS21, QS7, Quil A,  $\beta$ -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix,

15 particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or

20 suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol<sup>R</sup> to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the

25 combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL<sup>®</sup> adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

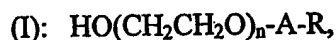


MPL<sup>®</sup> adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn<sup>®</sup>; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



wherein,  $n$  is 1-50,  $A$  is a bond or  $-\text{C}(\text{O})-$ ,  $R$  is  $\text{C}_{1-50}$  alkyl or Phenyl  $\text{C}_{1-50}$  alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein  $n$  is between 1 and 50, preferably 4-24, most preferably 9; the  $R$  component is  $\text{C}_{1-50}$ , preferably  $\text{C}_4\text{-C}_{20}$  alkyl and most preferably  $\text{C}_{12}$  alkyl, and  $A$  is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12<sup>th</sup> edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

5                   According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or  
10 maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

15                   Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In  
20 general, dendritic cells may be identified based on their typical shape (*stellate in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex*  
25 *vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

                  Dendritic cells and progenitors may be obtained from peripheral blood,  
30 bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc $\gamma$  receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including e.g., oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 5 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, 10 cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to 15 materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds 20 may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of 25 active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a 30 variety of dosages and treatment regimens may be desirable.

For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

10 In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds  
15 as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

20 Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and  
25 storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as  
30 lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

- 5 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered  
10 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml  
15 of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity  
20 standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative  
pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for  
25 example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be



administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption  
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase  
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the  
15 lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of  
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid  
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,  
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

5                   Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery  
10 systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

15                   In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

                  Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the  
20 present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1  $\mu\text{m}$ ) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for  
25 example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

### Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see, for example, Cheever et al., Immunological Reviews 157:177, 1997*).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g., intracutaneous,*

intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25  $\mu$ g to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the  
5 biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in  
10 the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c)  
15 comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding  
20 agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized  
25 binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as  
30 described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed



and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

10 To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with  
15 samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985,  
20 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a  
25 signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1  $\mu$ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the  
5 diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold*  
10 *Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules.  
15 PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold  
20 or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above  
25 for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1  $\mu$ g each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA<sup>+</sup> RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction  
5 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested,  
10 reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other  
15 normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously  
20 identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the  
25 corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

## EXAMPLE 2

## DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the  
5 representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor  
10 tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the  
15 first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was  
20 minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver,  
25 lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon  
30 and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,



small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be

over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatazis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence. Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is  
5 provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were  
10 generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign  
15 prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were  
20 negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful  
25 in the diagnosis of prostate cancer.

## EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC  
POLYPEPTIDES BY PCR-BASED SUBTRACTION

5 A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The  
10 resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA  
15 sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID  
20 NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences  
25 which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA  
30 sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones  
5 containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is  
10 provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine  
15 and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed  
20 comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor  
25 compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal  
30 prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those  
5 in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

10 PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in  
15 SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of  
20 the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172  
25 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids  
30 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified  
5 proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet  
10 activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorigenesis or activate a protease-  
15 activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully  
20 employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that  
25 P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences  
30 for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are



provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P

were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

5 Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

10 Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an  
15 ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

20 Subsequent studies led to the identification of a genomic region on chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential  
25 open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The  
30 full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

5 Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86%  
10 identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent  
15 amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

#### EXAMPLE 4

##### SYNTHESIS OF POLYPEPTIDES

20

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of  
25 conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid  
30 (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of

0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

5

### EXAMPLE 5

#### FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

10 A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide  
15 restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

20 The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate  
25 hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences  
30 which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

5 Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349,  
10 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant  
15 homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is  
20 provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of  
25 P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

5           The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

### EXAMPLE 6

## PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-A<sup>b</sup> binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL),  $2 \times 10^{-5}$  M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml  $\beta$ 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells ( $5 \times 10^5$ /ml) were restimulated with  $2.5 \times 10^6$ /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells



(Sherman et al, *Science* 258:815-818, 1992) and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed  
5 EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with  
10 P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

15 6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is  
20 derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding  
25 using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200  $\mu$ g/ml were added to  
30 cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,

CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

5 Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single  
10 cell suspensions prepared using a nylon mesh. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2µg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later cells ( $5 \times 10^5$ /ml) were restimulated  
15 with  $2.5 \times 10^6$ /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as  
20 shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were  
25 isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

## EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION  
WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred  
5 to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research  
Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012  
either intramuscularly or intradermally. The mice were immunized three times, with a  
two week interval between immunizations. Two weeks after the last immunization,  
immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator  
10 cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL  
activity was assessed against P501S transduced targets. Two out of 8 mice developed  
strong anti-P501S CTL responses. These results demonstrate that P501S contains at  
least one naturally processed HLA-A2-restricted CTL epitope.

15

## EXAMPLE 8

## ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate  
tumor polypeptide to recognize human tumor.

20

Human CD8<sup>+</sup> T cells were primed *in vitro* to the P2S-12 peptide (SEQ  
ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells  
according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75,  
1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to  
recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which  
25 were transduced to express the P502S gene in a γ-interferon ELISPOT assay (see  
Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells  
were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 µg/ml human β<sub>2</sub>-  
microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells  
were simultaneously assayed on autologous fibroblasts transduced with the P502S gene  
30 or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the

fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

#### EXAMPLE 9

##### ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

20

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GM-CSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays ( $^{51}\text{Cr}$  release) and interferon-gamma production (Interferon-gamma Elispot; *see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997*). The results of these assays are presented in Figures 6A and 6B.

10

## EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE  
PROSTATE-SPECIFIC ANTIGEN P703P

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100  $\mu\text{g}$  of p5 peptide together with 140  $\mu\text{g}$  of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte  
5 cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures,  
10 CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being  
15 recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived  
20 from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration  
25 of 0.25 microgram/ml. Pulsed DC were washed and plated at  $1 \times 10^4$  cells/well of 96-well V-bottom plates and purified CD4 T cells were added at  $1 \times 10^5$ /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2.  
30 Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by <sup>3</sup>H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized; *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E (a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E. coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cell lines were restimulated on the



appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A  
5 recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or  
10 were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of  
15 SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

### EXAMPLE 11

#### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN

#### IN PROSTATE

20

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences  
25 for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a  
30 frameshift in the open reading frame. The determined DNA sequence of this ORF is

provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

#### EXAMPLE 12

##### 15 GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- $\gamma$  ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3  $\mu$ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon- $\gamma$  when stimulated with P501S and CD80-transduced autologous  
5 fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- $\gamma$  in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

10 To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT  
15 assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid  
20 residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20)  
25 and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.

In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8<sup>+</sup> T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percoll gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4<sup>+</sup>, CD14<sup>+</sup> and CD16<sup>+</sup> populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8<sup>+</sup> T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8+ T cell line (referred to as 2A2) was identified that produced IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a  $\gamma$ -IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3+, CD8+ and CD4-.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in  $\gamma$ -IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8+ T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In  $\gamma$ -IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cw1, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were  
5 cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in  
10 ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the  
15 subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145  
20 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated  
25 cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line  
30 DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4  $\mu$ g/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using  $\gamma$ -IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4ug/ml or an irrelevant peptide at  $\mu$ g/ml were used as APC. T cell lines that demonstrated either specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.



From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1 µg/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.

**EXAMPLE 13****IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS****BY MICROARRAY ANALYSIS**

5 This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to  
10 non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-  
15 400) correspond to known sequences, as shown in Table I.

Table I  
Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-Iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

#### EXAMPLE 14

#### IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Table IIProstate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

- 5 Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the
- 10 Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters
- 15 (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table IV

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57



Table IIIProstate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

5           The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels  
10 of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes  
15 generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The  
20 sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being  
5 provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID  
10 NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are  
15 provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA  
20 sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

25

## EXAMPLE 16

## FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P  
30 fragment described above. One million colonies were plated on LB/Ampicillin plates.

439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that  
5 encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

#### EXAMPLE 15

##### 10 FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above  
15 was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-  
20 458 and 461-467) correspond to known sequences. Comparison of the determined

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The  
5 resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression  
10 was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen  
15 Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as  
20 Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to  
25 aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of  
30 the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

#### EXAMPLE 17

##### PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

##### a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 5 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD\_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as 10 described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against 15 P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant 20 protein.

#### c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to 25 as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The  
5 sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C  
10 fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense  
15 cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys S *E. coli* host cells in TB media for 2 h at room temperature. Expressed protein  
20 was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM  $\beta$ -Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectfully.

#### 25 b) Expression of P501S in Baculovirus

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the  $\alpha$  prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred  $\mu$ l of a master seed containing  $2.5 \times 10^8$  cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacin 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or  $9.3 \times 10^7$  cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacine 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; Histidine 0.1 g/l.

These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.



Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15 µl of GenePorter was diluted in 500 µl of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2 µg of plasmid DNA that was diluted in 500 µl of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast α prepro signal sequence. The natural signal sequence and first luminal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the α prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu<sup>+</sup> and His<sup>-</sup>. Expression of protein was induced by addition of either 500 µM or 250 µM of CuSO<sub>4</sub> at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD<sub>600</sub> 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

produce P501S antigen.  $\text{CuSO}_4$  addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC  
5 method). The fermentation was then supplemented by  $\text{CuSO}_4$  throughout the induction phase in order to maintain its concentration between 150 and 250  $\mu\text{M}$  in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western  
10 Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

15 The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

20

#### e) Expression of P703P in Baculovirus

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment  
25 (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the  
30 recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and  
 5 cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter  
 10 containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows:  
 (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> 6.4 g/l; Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O 2.05 mg/l; folic acid 0.54 mg/l; KH<sub>2</sub>PO<sub>4</sub> 8.25 g/l;  
 MnSO<sub>4</sub>·H<sub>2</sub>O 4.1 mg/l; inositol 540 mg; MgSO<sub>4</sub>·7H<sub>2</sub>O 4.69 g/l; H<sub>3</sub>BO<sub>3</sub> 5.17 m/l;  
 pyridoxine 68 mg/l; CaCl<sub>2</sub>·2H<sub>2</sub>O 0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l;  
 15 CoCl<sub>2</sub>·6H<sub>2</sub>O 0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l; FeCl<sub>3</sub>·6H<sub>2</sub>O 9.92 mg/l;  
 Riboflavin 0.13 mg/l; CuSO<sub>4</sub>·5H<sub>2</sub>O 0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68  
 mg/l; ZnSO<sub>4</sub>·7H<sub>2</sub>O 4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l;  
 Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding  
 20 of FFB004AA medium. The composition of the FFB004AA medium is as follows:  
 glucose 350 g/l; Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O 5.15 mg/l; folic acid 1.36 mg/l; KH<sub>2</sub>PO<sub>4</sub> 20.6 g/l;  
 MnSO<sub>4</sub>·H<sub>2</sub>O 10.3 mg/l; inositol 1350 mg/l; MgSO<sub>4</sub>·7H<sub>2</sub>O 11.7 g/l; H<sub>3</sub>BO<sub>3</sub> 12.9 m/l;  
 pyridoxine 170 mg/l; CaCl<sub>2</sub>·2H<sub>2</sub>O 2.35 g/l; KI 2.6 mg/l; thiamine 170 g/l; NaCl 0.15 g/l;  
 CoCl<sub>2</sub>·6H<sub>2</sub>O 2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l; FeCl<sub>3</sub>·6H<sub>2</sub>O 24.8 mg/l;  
 25 riboflavin; 0.33 mg/l; CuSO<sub>4</sub>·5H<sub>2</sub>O 1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170  
 mg/l; ZnSO<sub>4</sub>·7H<sub>2</sub>O 10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low (□50 mg/L)  
 in order to minimize ethanol production by fermentation. This was achieved by limiting  
 the development of the microorganism using a limited glucose feed rate. The Standard  
 30 biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500μM CuSO<sub>4</sub> in order to

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction  
5 the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin +  
10 chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682,  
15 respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were  
20 those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL  
25 competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin  
30 and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after  
5 induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

10

#### H) EXPRESSION OF A P703P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
15 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

20

#### I) EXPRESSION OF A P705P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
25 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

30

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

5           The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site  
10 for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing  
15 confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3  
20 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

25           The antigen P775P contains multiple open reading frames (ORF). The third ORF, encoding the protein of SEQ ID NO: 483, has the best emotif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room



**J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN *E. COLI***

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

10

**EXAMPLE 18****PREPARATION AND CHARACTERIZATION OF ANTIBODIES****AGAINST PROSTATE-SPECIFIC POLYPEPTIDES**

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**a) Preparation and Characterization of Polyclonal Antibodies against P703P,****P504S and P509S**

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

20

Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

25

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

5

Table VIsotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant ( $\mu\text{g/ml}$ )
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1  $\mu\text{g/ml}$ , followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000  
5 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H<sub>2</sub>SO<sub>4</sub> and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity  
10 to the appropriate antigen.

**b) Preparation and Characterization of Antibodies against P501S**

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO:  
15 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

20 Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody  
25 component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson Immunoresearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with P501S or HLA-B8' as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5 In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well  
10 microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was  
15 followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with  
20 supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds  
25 to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to  
30 cell surface epitopes. Cells stably transfected with a control plasmid were employed as

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

c) Preparation and Characterization of Antibodies against P503S

10 A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at  
15 Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptrl attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk<sup>-/-</sup> cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with



a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur  
5 fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder,  
10 ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall  
15 bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with  
20 each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa  
25 species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

5

## EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND  
CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10 This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-  
15 P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the  
20 predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino  
25 Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of  
30 P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,

recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases, including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-  
5 PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g  
10 (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the  
15 corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment  
20 (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng -  
25 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As  
30 shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed, incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

labeled with  $^{32}\text{P}$  using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 0.001 M  $\text{Na}_2\text{EDTA}$ ), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

## EXAMPLE 20

### PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H<sub>2</sub>SO<sub>4</sub> and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server



cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

- 5           The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml
- 10 chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the
- 15 cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl
- 20 pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing
- 25 FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

## EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN  
PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

- 5           Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman™ procedure using both gene specific primers and probes to determine the levels of gene expression.
- 10           Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0
- 15           and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman™ procedure but extending to 50 cycles using
- 20           forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and  $\beta$ -actin signal. The remaining 2 samples had no detectable  $\beta$ -actin or P501S. No P501S signal was observed in the four normal blood samples tested.

25

## EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN  
SCID MOUSE-PASSAGED PROSTATE TUMORS

- 30           When considering the effectiveness of antigens in the treatment of prostate cancer, the continued presence of the antigens in tumors during androgen

ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed  
5 from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was  
10 present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

#### EXAMPLE 23

##### 15 ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0  
20 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

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#### EXAMPLE 24

##### CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

30 T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from  $2 \times 10^6$  cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Furthermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC---ATGTCACCTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC---ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was  
5 shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338),

From the foregoing it will be appreciated that, although specific  
embodiments of the invention have been described herein for purposes of illustration,  
10 various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

## What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

- (d) sequences encoded by a polynucleotide of claim 1;
- (e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.



8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1; and
- (c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 11; and
- (f) antigen presenting cells that express a polypeptide according to

claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.

17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

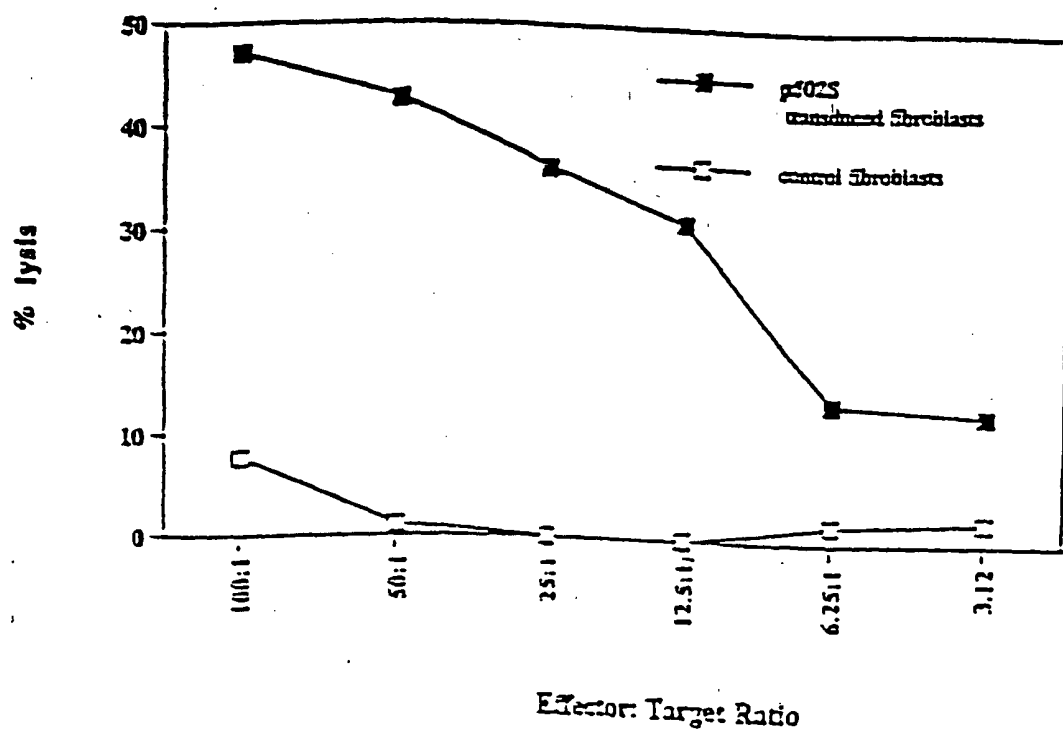


Fig. 1

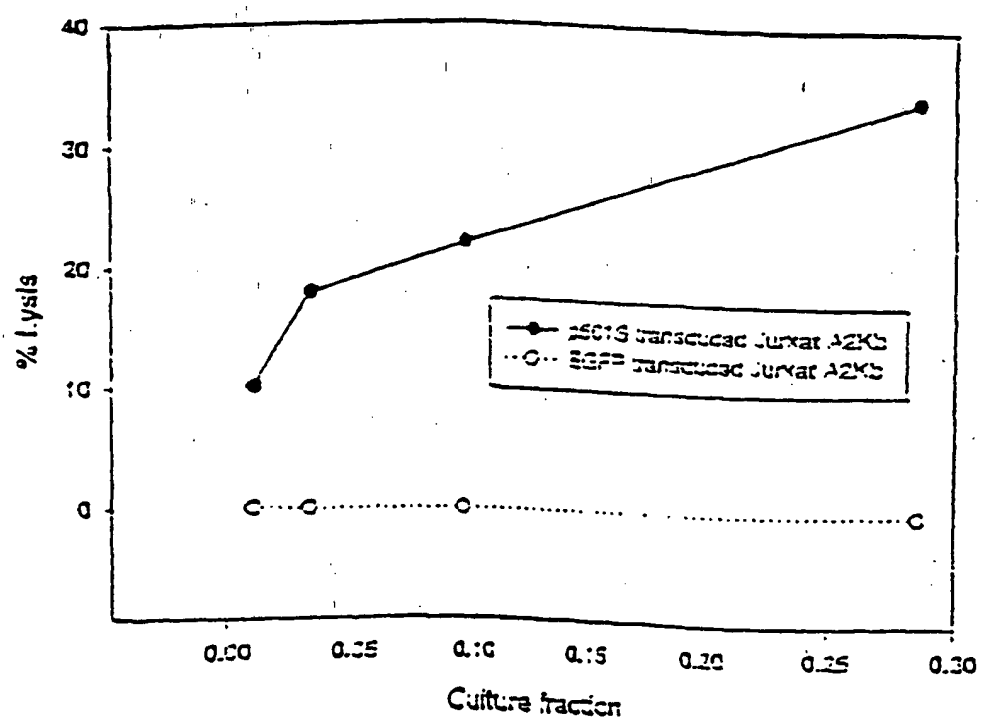


Fig. 5

# Genomic Map of (5) Corlxa Candidate Genes

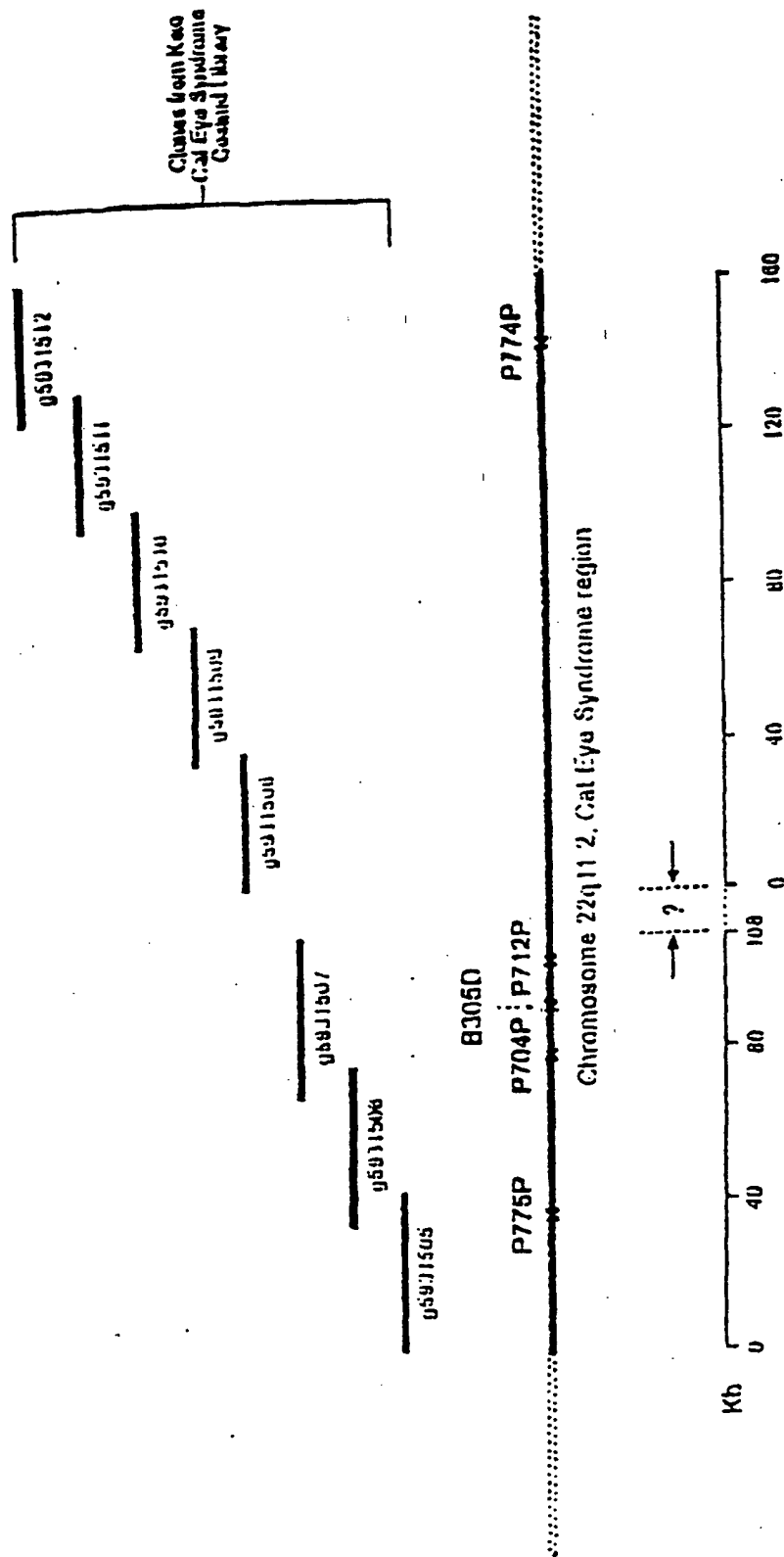
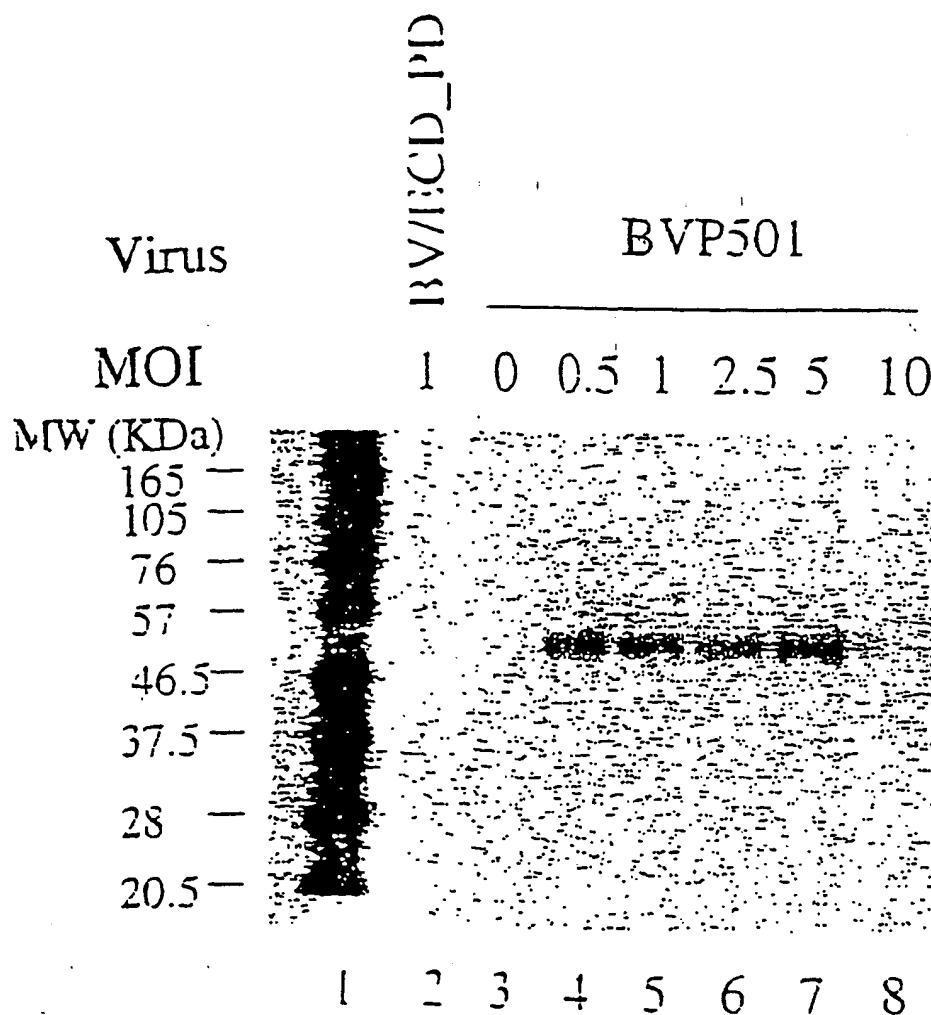


Fig. 10

# Expression of P501S by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD\_PD (lane 2), without virus (lane 3), or with recombinant baculovirus for P501 at different MOIs (lane 4-8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E3-G4D3). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

Fig. 7

Fig. 8

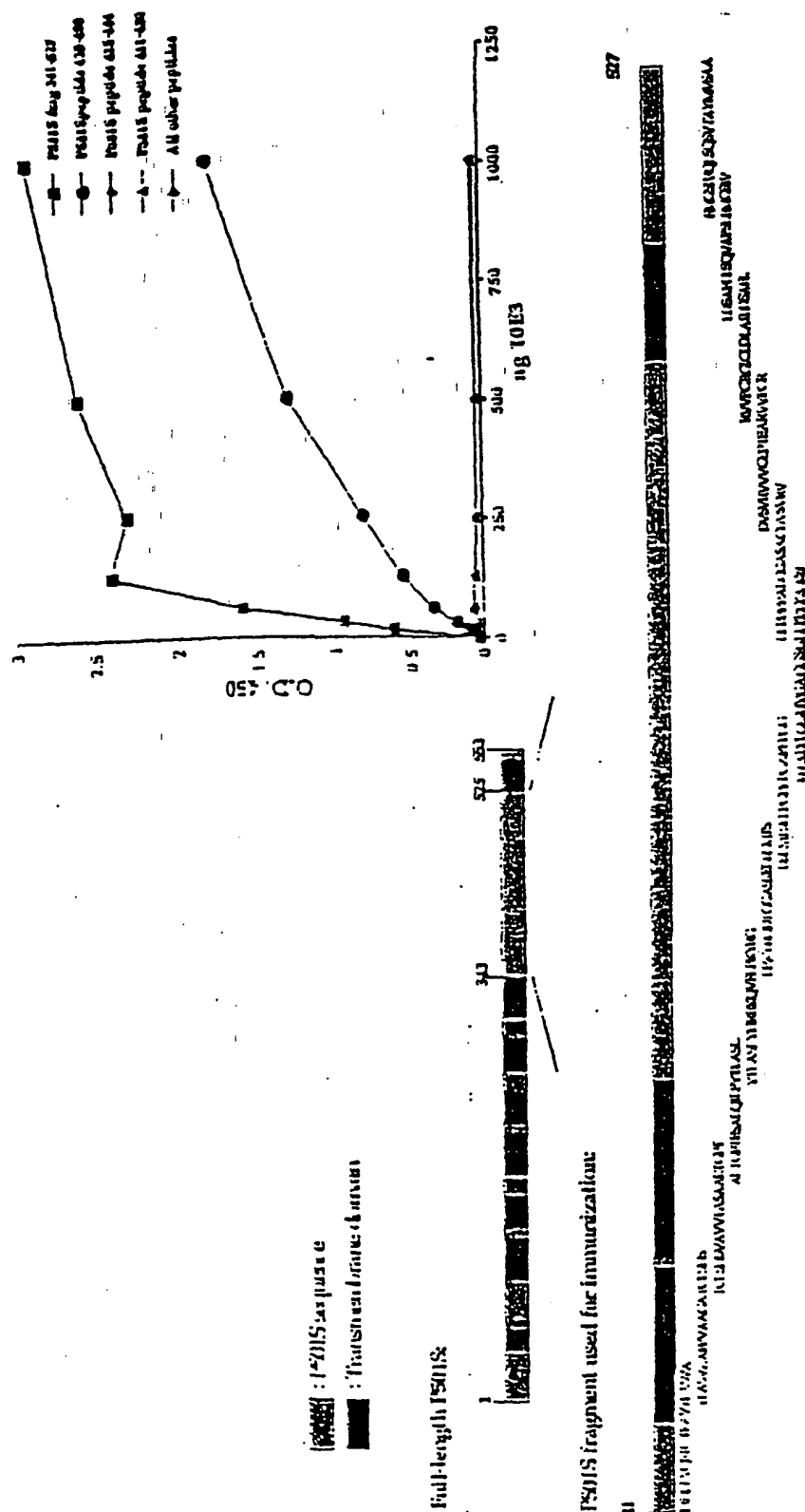




FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity

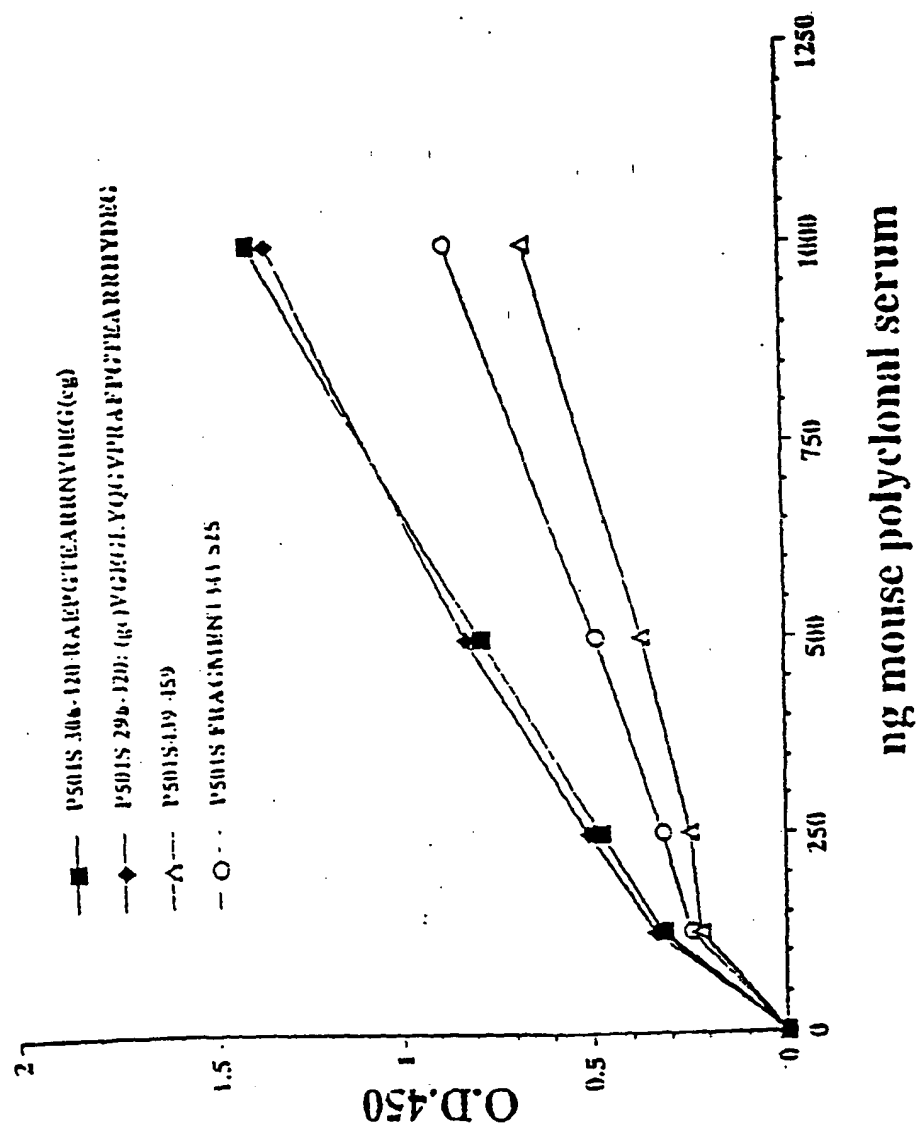


Fig. 11

## SEQUENCE LISTING

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 Smithkline Beechan Biologicals S.A.  
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 Dillon, Davin C.  
 Mitcham, Jennifer L.  
 Harlocker, Susan L.  
 Jiang, Yuqui  
 Reed, Steven G.  
 Kalos, Michael D.  
 Fanger, Gary R.  
 Retter, Marc W.  
 Stolk, John A.  
 Day, Craig H.  
 Skeiky, Yasir A.W.  
 Wang, Aijun  
 Meagher, Medeleine Joy  
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<120> COMPOSITIONS AND METHODS FOR THE THERAPY AND  
 DIAGNOSIS OF PROSTATE CANCER

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ttcatggctg ttggagcaat agaaccaccag ttctacgagc tgctgatcaa aggacttggg	120
ctaaagtctg atgaacttcc caatcagatg agcatggatg attggccaga aatgaagaag	180
aagtttgacg atgtatttgc aaagaagacg aaggcagagt ggtgtcaaat ctttgacggc	240
acagatgcct gtgtgactcc ggttctgact tttgaggagg ttgttcatca tgatcacaac	300
aaggaacggg gctcgtttat caccagttag gagcaggacg tgagcccccg ccctgcacct	360
ctgctgttaa acaccaccag catcccttct ttcaaaaggg atccactagt tctagaagcg	420
ggcgccaccg cgggtggagct ccagcttttg ttcccttttag tgagggttaa ttgcgcgctt	480
ggcgtaatca tgggtcatagc tgtttcctgt gtgaaattgt tatccgctca caattccccc	540
aacatacgag ccggaacata aagtgttaag cctgggggtgc ctaatgantg agctaactcn	600
cattaattgc gttgcgctca ctgcccgtt tccagtcggg aaaactgtcg tgccactgcn	660
ttantgaatc ngccaccccc cgggaaaagg cggttgcntt ttgggcctct tccgctttcc	720
tcgctcattg atcctngcnc ccggtcttcg gctgcggnga acggttcaact cctcaaaggc	780
ggtntnccgg ttatccccaa acnggggata cccnga	816

<210> 3  
 <211> 773  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(773)  
 <223> n = A,T,C or G

<400> 3	
cttttgaaag aagggatggc tggggtgttt aacagcagag gtgcagggcg ggggctcacg	60
tctgtctcct cactggtgat aaacgagccc cgttccttgt tgtgatcatg atgaacaacc	120
tctcaaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac	180
tctgccttcg tcttctttgc aaatacatct gcaaaacttct tcttcatttc tggccaatca	240
tccatgctca tctgattggg aagttcacat gactttagtc canntccttt gatcagcagc	300
tcgtagaact ggggttctat tgcctcaaca gccatgaatt ccccatctgc tgtcctgtaa	360
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg gggccggtac	420
ccaattcgcc ctatantgag tcgtattacg cgcgctcact ggccgtcgtt ttacaacgtc	480
gtgactggga aaaccctggg cgttaccaac ttaatcgctt tgcagcacat ccccctttcg	540
ccagctgggc gtaatanaga aaaggcccg cccgatcgcc cttccaacag ttgcgcacct	600
gaatgggnaa atgggacccc cctgttaccg cgcattnaac ccccgcnagg tttngttgtt	660
acccccacnt nnaccgctta cactttgcca gcgccttanc gcccgtccc tttcnccttt	720
cttcccttcc tttcncncn ctttcccccg gggtttcccc cntcaaacc cna	773

<210> 4  
 <211> 828  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(828)

<223> n = A,T,C or G

<400> 4

cctcctgagt	cctactgacc	tgtgctttct	ggtgtggagt	ccagggctgc	taggaaaagg	60
aatgggcaga	cacaggtgta	tgccaatgtt	tctgaaatgg	gtataatttc	gtcctctcct	120
tcggaacact	ggctgtctct	gaagacttct	cgctcagttt	cagtgaggac	acacacaaag	180
acgtgggtga	ccatgttggt	tgtgggggtc	agagatggga	gggggtggggc	ccaccctgga	240
agagtggaca	gtgacacaag	gtggacactc	tctacagatc	actgaggata	agctggagcc	300
acaatgcata	aggcacacac	acagcaagga	tgacnctgta	aacatagccc	acgctgtcct	360
gngggcactg	ggaagcctan	atnaggccgt	gagcanaaag	aaggggagga	tccactagtt	420
ctanagcggc	cgccaccgcg	gtgganctcc	ancttttgtt	cccttttagt	aggggttaatt	480
gcgcgcttgg	cntaatcatg	gtcatanctn	tttctgtgtg	gaaattgtta	tccgctcaca	540
attccacaca	acatacganc	cggaacata	aantgtaaac	ctgggggtgcc	taatgantga	600
ctaactcaca	ttaattgcgt	tgcgctcact	gcccgccttc	caatcnggaa	acctgtcttg	660
ccncttgcat	tnatgaatcn	gccaaacccc	ggggaaaagc	gtttgcgttt	tgggcgctct	720
tccgcttctc	cnctcantta	ntccctncnc	tcggtcattc	cggctgcngc	aaaccgggtc	780
accnctcca	aaggggggtat	tccggtttcc	ccnaatccgg	gganancc		828

<210> 5

<211> 834

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(834)

<223> n = A,T,C or G

<400> 5

tttttttttt	tttttactga	tagatggaat	ttattaagct	tttcacatgt	gatagcacat	60
agttttaatt	gcatccaaag	tactaacaaa	aactctagca	atcaagaatg	gcagcatgtt	120
attttataac	aatcaacacc	tgtggctttt	aaaatttgg	tttcataaga	taattttatac	180
tgaagtaaat	ctagccatgc	ttttaaaaaa	tgcttttagt	cactccaagc	ttggcagtta	240
acatttggca	taaacaataa	taaaacaatc	acaattttaat	aaataacaaa	tacaacattg	300
taggccataa	tcatatacag	tataaggaaa	aggtggtagt	gttgagtaag	cagttattag	360
aatagaatac	cttggcctct	atgcaaatat	gtctagacac	tttgattcac	tcagccctga	420
cattcagttt	tcaaagtagg	agacaggttc	tacagtatca	ttttacagtt	tccaacacat	480
tgaaaacaag	tagaaaatga	tgagttgatt	tttattaatg	cattacatcc	tcaagagtta	540
tcaccaaccc	ctcagttata	aaaaattttc	aagttatatt	agtcataata	cttgggtgtgc	600
ttattttaaa	ttagtgtctaa	atggattaag	tgaagacaac	aatgggtccc	taatgtgatt	660
gatattggtc	atttttacca	gcttctaaat	ctnaactttc	aggcttttga	actggaacat	720
tgnatnacag	tgttccanag	ttincaacct	ctggaacatt	acagtgtgct	tgattcaaaa	780
tgttattttg	ttaaaaatta	aattttaacc	tggtggaaaa	ataatttgaa	atna	834

<210> 6

<211> 818

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(818)

<223> n = A,T,C or G

&lt;400&gt; 6

tttttttttt	tttttttttt	aagaccctca	tcaatagatg	gagacataca	gaaatagtca	60
aaccacatct	acaaaatgcc	agtatcaggc	ggcgggttcg	aagccaaagt	gatgtttgga	120
tgtaaagtga	aatattagtt	ggcggatgaa	gcagatagtg	aggaaagttg	agccaataat	180
gacgtgaagt	ccgtggaagc	ctgtggctac	aaaaaatggt	gagccgtaga	tgccgtcgga	240
aatggtgaag	ggagactcga	agtactctga	ggcttgtagg	agggtaaaaat	agagacccag	300
taaaattgta	ataagcagtg	cttgaattat	ttgggttcgg	ttgttttcta	ttagactatg	360
gtgagctcag	gtgattgata	ctcctgatgc	gagtaatacg	gatgtgttta	ggagtgggac	420
ttctagggga	tttagcgggg	tgatgcctgt	tggggggccag	tgccctocta	gttggggggt	480
aggggctagg	ctggagtggt	aaaaggctca	gaaaaatcct	gcgaagaaaa	aaacttctga	540
ggtaataaat	aggattatcc	cgtatcgaag	gccttttttg	acaggtggtg	tgtggtggcc	600
ttggtatgtg	ctttctcgtg	ttacatcgcg	ccatcattgg	tatatggtta	gtgtgttggt	660
ttantangg	ctantatgaa	gaacttttgg	antggaatta	aatcaatngc	ttggccggaa	720
gtcattanga	nggctnaaaa	ggccctgtta	ngggtctggg	ctnggtttta	cccnacccat	780
ggaatncncc	ccccggacna	ntgnatccct	attcttaa			818

&lt;210&gt; 7

&lt;211&gt; 817

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(817)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 7

tttttttttt	tttttttttt	tggctctaga	gggggtagag	gggggtgctat	agggtaaata	60
cggggccctat	ttcaaagatt	tttaggggaa	ttaattctag	gacgatgggt	atgaaactgt	120
ggtttgtctc	acagatttca	gagcattgac	cgtagtatac	ccccggtcgt	gtagcgggtga	180
aagtggtttg	gttttagacgt	ccgggaattg	catctgtttt	taagcctaata	gtggggacag	240
ctcatgagt	caagacgtct	tgtgatgtaa	ttattatacn	aatgggggct	tcaatcggga	300
gtactactcg	attgtcaacg	tcaaggagtc	gcaggtcgcc	tggttctagg	aataatgggg	360
gaagtatgta	ggaattgaag	attaatccgc	cgtagtcggt	gttctcctag	gttcaatacc	420
attggtggcc	aattgatttg	atggtaaagg	gagggatcgt	tgaactcgtc	tgttatgtaa	480
aggatncctt	ngggatggga	aggcnatnaa	ggactangga	tnaatggcgg	gcangatatt	540
tcaaacngtc	tctanttcct	gaaacgtctg	aaatgttaat	aanaattaan	tttngttatt	600
gaatnttng	gaaaagggct	tacaggacta	gaaaccaa	angaaaanta	atnntaang	660
cnttatcntn	aaagtnata	accnctccta	tnatcccacc	caatngnatt	ccccacnncn	720
acnattggat	nccccanttc	canaaanggc	cncctcccg	tgnannccnc	cttttgttcc	780
cttnantgan	ggttattcnc	ccctngcntt	atcance			817

&lt;210&gt; 8

&lt;211&gt; 799

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(799)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 8

catttccggg	tttactttct	aaggaaagcc	gagcggaagc	tgctaacgtg	ggaatcggtg	60
cataaggaga	actttctgct	ggcacgcgct	agggacaagc	gggagagcga	ctccgagcgt	120
ctgaagcgca	cgtcccagaa	ggtggacttg	gcactgaaac	agctgggaca	catccgcgag	180
tacgaacagc	gactgaaagt	gctggagcgg	gaggtccagc	agtgtagccg	cgtcctgggg	240

tggttgccg	angcctganc	cgctctgcct	tgctgcccc	angtgggccc	ccaccccctg	300
acctgcctg	gtccaaacac	tgagccctgc	tgccggactt	caagganaac	ccccacang	360
ggattttgct	cctanantaa	ggctcatctg	ggcctcgccc	ccccacctg	gttggccttg	420
tctttgagt	gagcccatg	tccatctggg	ccactgtcng	gaccacctt	ngggagtgtt	480
ctccttaca	ccacannatg	cccggctcct	cccggaaacc	antccancc	tgngaaggat	540
caagnccctg	atccactnnt	nctanaaccg	gccnccnccg	cngtggaaacc	cnccttntgt	600
tccttttct	tnagggttaa	tnnccgcttg	gccttnccan	ngtccnccn	ntttccnnt	660
gttnaaattg	ttangcnccc	nccnntccn	cnnccnccn	cccgaaccnn	anntnnann	720
ncctgggggt	nccnccngat	tgaccncc	nccctntant	tgcnttnggg	nncnntgccc	780
ctttccctct	nggganncg					799

<210> 9  
 <211> 801  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(801)  
 <223> n = A,T,C or G

<400> 9						
acgccttgat	cctcccaggc	tggtgactgt	tctgggagga	gccgggcatg	ctgtggtttg	60
taangatgac	actcccaaag	gtgtcctga	cagtggccca	gatggacatg	gggtcacct	120
caaggacaag	gccaccagg	gcgggggccg	aagccacat	gacccctact	ctatgagcaa	180
aatccctgt	gggggcttct	ccttgaagtc	cgccancagg	gctcagtctt	tggaaccang	240
caggtcatgg	ggtgtngnc	caactggggg	ccncaacgca	aaanggcnc	gggcctcngn	300
cacccatccc	angacgcggc	tacactnctg	gacctcccnc	tccaccactt	tcatgcgctg	360
ttcntaccg	cgnatntgtc	ccanctgttt	cngtgcenac	tccancttct	nggacgtgcg	420
ctacatacgc	cggantcnc	netcccgtt	tgccctatc	cacgtncan	caacaaattt	480
cncctantg	caccnattcc	cacntttnnc	agntttccnc	nncngcttc	cttntaaaag	540
ggttganccc	cggaaaatnc	cccaaagggg	gggggcccng	tacccaaactn	ccccctnata	600
gctgaantcc	ccatnaccnn	gnctcnatgg	ancntccnt	tttaannacn	ttctnaactt	660
gggaanance	ctcgnccntn	ccccnttaa	tccnccctg	cnangnnct	ccccnntcc	720
nccnntntg	gcntntnann	cnaaaaaggc	ccnnnancaa	tctcctnnn	cctcanttgc	780
ccanccctcg	aatcgccn	c				801

<210> 10  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 10						
cagtctatnt	ggccagtgtg	gcagctttcc	ctgtggctgc	cggtgccaca	tgctgtccc	60
acagtgtggc	cgtggtgaca	gcttcagccg	ccctcaccgg	gttcaccttc	tcagccctgc	120
agatccctgc	ctacacactg	gcctccctct	accaccggga	gaagcagggtg	ttcctgccca	180
aataccgagg	ggacactgga	ggtgctagca	gtgaggacag	cctgatgacc	agcttcctgc	240
caggccctaa	gcctggagct	cccttcccta	atggacacgt	gggtgctgga	ggcagtggcc	300
tgctcccacc	tccaccgcg	ctctgcccgg	cctctgcctg	tgatgtctcc	gtacgtgtgg	360
tggtgggtga	gccaccgan	gccagggtgg	ttccggggccg	gggcatctgc	ctggacctcg	420
ccatccctga	tagtgcttcc	tgctgtccca	ngtggcccca	tccctgttta	tggttccat	480
tgtccagctc	agccagtctg	tactgccta	tatggtgtct	gccgcaggcc	tggttctggt	540
cccatttact	ttgctacaca	ggtantattt	gacaagaacg	anttgcccaa	atactcagcg	600

ttaaaaaatt	ccagcaacat	tgggggtgga	aggcctgcct	cactgggtcc	aactccccgc	660
tcctgttaac	cccatggggc	tgccggcttg	gccgccaatt	tctgttgctg	ccaaantnat	720
gtggctctct	gctgccacct	gttgetggct	gaagtgcnta	cngcncanct	nggggggtng	780
ggngttccc						789

<210> 11  
 <211> 772  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(772)  
 <223> n = A,T,C or G

<400> 11						
cccaccctac	ccaaatatta	gacaccaaca	cagaaaagct	agcaatggat	tcccttctac	60
tttgtaaata	aaataagtta	aatattttaa	tgccctgtgc	tctgtgatgg	caacagaagg	120
accaacaggc	cacatcctga	taaaaggtaa	gaggggggtg	gatcagcaaa	aagacagtgc	180
tgtgggctga	ggggacctgg	ttcttgtgtg	ttgcccctca	ggactcttcc	cctacaaata	240
actttcatat	gttcaaactc	catggaggag	tgtttcatcc	tagaaactcc	catgcaagag	300
ctacattaaa	cgaagctgca	ggttaagggg	cttanagatg	ggaaaccagg	tgactgagtt	360
tattcagctc	ccaaaaaccc	ttctctaggt	gtgtctcaac	taggaggcta	gctgttaacc	420
ctgagcctgg	gtaatccacc	tgacagatcc	ccgcattcca	gtgcatggaa	cccttctggc	480
ctccctgtat	aagtccagac	tgaaaccccc	ttggaaggnc	tccagtcagg	cagccctana	540
aactggggaa	aaaagaaaag	gacgccccan	ccccagctg	tgcantacg	cacctcaaca	600
gcacaggggtg	gcagcaaaaa	aaccacttta	ctttggcaca	aacaaaaact	ngggggggca	660
accccgccac	cccnangggg	gttaacagga	ancngggnaa	cntggaaccc	aattnaggca	720
ggcccncac	ccnaatntt	gctgggaaat	tttctctccc	ctaaattntt	tc	772

<210> 12  
 <211> 751  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 12						
gccccaatc	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtanggtg	agtccctcaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atggtggtgt	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttcatggca	300
ggcactacca	gcaacgtcag	ggaagtgtct	agccattgtg	gtgtacacca	aggcgaccac	360
agcagctgcn	acctcagcaa	tgaagatgan	gaggangatg	aagaagaacg	tcnctagggc	420
acacttgctc	tcagtcttan	caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cncggctgct	gatgaagaaa	tnaccccneg	ttgacaaaact	tgcatggcac	tggganccac	540
agtggccocna	aaaatcttca	aaaaggatgc	cccactnatt	gaccccccaa	atgccacttg	600
ccaacagggg	ctgccccacn	cncnnaacga	tgancnatt	gnacaagatc	tncntggtct	660
tnatnaacnt	gaaccctgcn	tngtggctcc	tgttcaggnc	cnnngcctga	cttctnaann	720
aangaactcn	gaagncccca	cngganannc	g			751

<210> 13  
 <211> 729  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

gagccaggcg	tccctctgcc	tgcccactca	gtggcaacac	ccgggagctg	ttttgtcctt	60
tgtggancct	cagcagtncc	ctctttcaga	actcantgcc	aagancctg	aacaggagcc	120
accatgcagt	gcttcagctt	cattaagacc	atgatgatcc	tcttcaattt	gtcatcctt	180
ctgtgtggtg	cagccctggt	ggcagtgggc	atctgggtgt	caatcgatgg	ggcatcctt	240
ctgaagatct	tggggccact	gtcgtccagt	gccatgcagt	ttgtcaacgt	gggtacttc	300
ctcatcgag	ccggcggtgt	ggtcttagct	ctaggtttcc	tgggctgcta	tggtgctaag	360
actgagagca	agtgtgccct	cgtgacgttc	ttcttcatcc	tcctcctcat	cttcattgct	420
gaggttgcaa	tgctgtggtc	gccttggtgt	acaccacaat	ggctgagcac	ttcctgacgt	480
tgctggaat	gcctgccatc	aanaaaagat	tatgggttcc	caggaanact	tcactcaagt	540
ggttgaacac	caccatgaaa	gggctcaagt	gctgtggctt	cnnccaacta	tacggatttt	600
gaagantcac	ctacttcaaa	gaaaanagt	cctttcccc	atttctgttg	caattgacaa	660
acgtcccaa	cacagccaat	tgaaaacctg	cacccaaccc	aaanggtcc	ccaaccanaa	720
attnaagg						729

<210> 14

<211> 816

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(816)

<223> n = A,T,C or G

<400> 14

tgtcttctct	caaagttggt	cttgttgcca	taacaaccac	cataggtaaa	gcgggcgcag	60
tggtcgctga	aggggttgta	gtaccagcgc	gggatgctct	ccttgcagag	tcctgtgtct	120
ggcagggtcca	cgcagtgccc	tttgtcactg	gggaaatgga	tgcgctggag	ctcgtcaaag	180
ccactcgtgt	atctttcaca	ggcagcctcg	tccgacgcgt	cggggcagtt	gggggtgtct	240
tcacactcca	ggaaactgtc	natgcagcag	ccattgtctg	agcggaaactg	ggtgggctga	300
cangtgccag	agcacactgg	atggcgcctt	tccatgnnan	gggccctgng	ggaaagtccc	360
tgancccan	anctgcctct	caaangcccc	accttgacac	ccccgacagg	ctagaatgga	420
atctttcttc	cgaaaggtag	ttnttcttgt	tgcccaancc	ancccntaa	acaaactctt	480
gcanatctgc	tccngggggg	tctantacc	ancgtgggaa	aagaacccca	ggcngcgaac	540
caancttggt	tggatncgaa	gcnataatct	ncntttctgc	ttggtggaca	gcaccantna	600
ctgtnnanct	ttagnccntg	gtcctcntgg	gttgnncttg	aacctaatcn	ccnntcaact	660
gggacaagg	aantngccnt	cctttnaatt	cccnanctn	ccccctggtt	tgggggtttt	720
cncnctccta	ccccagaaan	nccgtgttcc	cccccaacta	ggggccnaaa	ccnnttnttc	780
cacaacctn	ccccacccac	gggttcngnt	ggttng			816

<210> 15

<211> 783

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(783)

<223> n = A,T,C or G



&lt;400&gt; 15

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atgtggaaaa	cacagattgg	cgcctactgc	ggggtgacac	ggatgtcagg	gtagagagga	120
aagacccaaa	ccaggtggaa	ctgtggggac	tcaaggaang	cacctacctg	ttccagctga	180
cagtgaactag	ctcagaccac	ccagaggaca	cggccaacgt	cacagtcact	gtgctgtcca	240
ccaagcagac	agaagactac	tgcctcgcac	ccaacaangt	gggtcgctgc	cggggctctt	300
tcccacgctg	gtactatgac	cccacggagc	agatctgcaa	gagtttcggt	tatggagggt	360
gcttgggcaa	caagaacaac	taccttcggg	aagaagagt	cattctancc	tgctnggggt	420
tgcaaggtgg	gcctttgana	ngcanctctg	gggctcangc	gactttcccc	cagggcccct	480
ccatggaaag	gcgccatcca	ntgttctctg	gcacctgtca	gccaccccag	ttccgctgca	540
ncaatggctg	ctgcacnac	antttcctng	aattgtgaca	acacccccca	ntgcccccaa	600
ccctcccaac	aaagcttcgc	tgtnaaaaaa	tacnccantt	ggcttttnac	aaacncccgg	660
cncctccttt	ttccccnntn	aacaaagggc	nctngccttt	gaactgccc	aaacccnggaa	720
ctnccnngg	aaaaantncc	ccccctgggt	cctnnaancc	cctccnccna	anctncccc	780
ccc						783

&lt;210&gt; 16

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(801)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 16

gcccccaattc	cagctgccac	accaccccacg	gtgactgcat	tagttcggat	gtcatataaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttgg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtagggtg	agtctcaaaa	atccgtatag	ttggtgaagc	cacagcactt	gagccctttc	240
atggtgtgt	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	gaagtgtctca	gccattgtgg	tgtacaccaa	ggcgaccaca	360
gcagctgcaa	cctcagcaat	gaagatgagg	aggaggtatga	agaagaacgt	cncgagggca	420
cacttgctct	ccgtcttagc	accatagcag	cccangaaac	caagagcaaa	gaccacaacg	480
ccngctgcga	atgaaagaaa	ntaccacag	tgacaaactg	catggccact	ggacgacagt	540
tgggccgaan	atcttcagaa	aagggatgcc	ccatcgattg	aacaccana	tgcccactgc	600
cnacagggct	gcnccnncn	gaaagaatga	gccattgaag	aaggatcctc	ntggctttaa	660
tgaactgaaa	ccntgcatgg	tggccctgt	tcagggctct	tggcagtga	ttctganaaa	720
aaggaacngc	ntnagcccc	ccaaangana	aaacaccccc	gggtgttgcc	ctgaattggc	780
ggccaaggan	ccctgccccn	g				801

&lt;210&gt; 17

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(740)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 17

gtgagagcca	ggcgtccctc	tgcctgcca	ctcagtggca	acacccggga	gctgttttgt	60
cctttgtgga	gcctcagcag	ttccctcttt	cagaactcac	tgccaagagc	cctgaacagg	120
agccaccatg	cagtgttca	gcttcattaa	gaccatgatg	atcctcttca	atttgtcat	180
ctttctgtgt	ggtgcagccc	tggtggcagt	gggcatctgg	gtgtcaatcg	atggggcatc	240
ctttctgaag	atcttcgggc	cactgtcgtc	cagtgcctatg	cagtttgtca	acgtgggcta	300

cttcctcatc	gcagccggcg	ttgtggtctt	tgctcttggt	ttcctgggct	gctatgggtgc	360
taagacggag	agcaagtgtg	ccctcgtgac	gttcttcttc	atcctcctcc	tcattcttcat	420
tgctgaagtt	gcagctgctg	tggtcgcctt	ggtgtacacc	acaatggctg	aaccattcct	480
gacgttgctg	gtantgcctg	ccatcaanaa	agattatggg	ttcccaggaa	aaattcactc	540
aantntggaa	caccnccatg	aaaagggtc	caatttctgn	tggtctcccc	aactataccg	600
gaattttgaa	agantcnccc	tacttccaaa	aaaaaanant	tgcttttnc	ccnttctgt	660
tgcaatgaaa	acntcccaan	acngccaatn	aaaacctgcc	cnnncaaaaa	ggntcncaaa	720
caaaaaaant	nnaagggttn					740

<210> 18  
 <211> 802  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(802)  
 <223> n = A,T,C or G

<400> 18						
ccgctgggtg	cgctgggtcca	gnagnaccac	gaagcacgtc	agcatacaca	gcctcaatca	60
caaggtcttc	cagctgccgc	acattacgca	gggcaagagc	ctccagcaac	actgcatatg	120
ggatacactt	tactttagca	gccagggtga	caactgagag	gtgtcgaagc	ttattcttct	180
gagcctctgt	tagtgaggga	agattccggg	cttcagctaa	gtagtcagcg	tatgtcccat	240
aagcaaacac	tgtgagcagc	cggaaggtag	aggcaaagtc	actctcagcc	agctctctaa	300
cattgggcat	gtccagcagt	tctccaaaca	cgtagacacc	agnggcctcc	agcacctgat	360
ggatgagtgt	ggccagcgct	gcccccttgg	ccgacttggc	taggagcaga	aattgctcct	420
ggttctgccc	tgtaaccttc	acttcgcgac	tcateactgc	actgagtgtg	ggggacttgg	480
gctcaggatg	tccagagacg	tggttcggcc	ccctcnctta	atgacaccgn	ccanncaacc	540
gtcggctccc	gccgantgng	ttcgtcgtnc	ctgggtcagg	gtctgctggc	cnctacttgc	600
aancttctgc	nggcccattg	aattcaccnc	accggaactn	gtangatcca	ctnnttctat	660
aaccgngcgc	caccgcnnt	ggaactccac	tcttnttnc	tttacttgag	gggttaaggtc	720
acccttnncg	ttaccttggt	ccaaaccntn	ccntgtgtcg	anatngtnaa	tcnggncna	780
tnccanccnc	atangaagcc	ng				802

<210> 19  
 <211> 731  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(731)  
 <223> n = A,T,C or G

<400> 19						
cnaagcttcc	aggtnacggg	ccgcnaancc	tgaccnagg	tancanaang	cagnncgcg	60
gagcccaccg	tcacngngng	gngtctttat	nggagggggc	ggagccacat	cnctggacnt	120
cntgacccca	actccccncc	ncncantgca	gtgatgagtg	cagaactgaa	ggtnacgtgg	180
caggaaccaa	gancaaannc	tgctccnntc	caagtcggcn	nagggggcgg	ggctggccac	240
gncatecent	cnagtgetgn	aaagccccnn	cctgtctact	tgtttgaga	acngcnnga	300
catgcccagn	gttanataac	nggcngagag	tnantttgcc	tctcccttcc	ggctgcgean	360
cgngtntgct	tagnggacat	aacctgacta	cttaactgaa	cccnngaate	tnccnccct	420
ccactaagct	cagaacaaaa	aacttcgaca	ccactcantt	gtcacctgnc	tgctcaagta	480
aagtgtaccc	catncccaat	gtntgctnga	ngctctgncc	tgcnttangt	tcggctctgg	540
gaagacctat	caattnaagc	tatgtttctg	actgctctt	gctccctgna	acaancnacc	600
cnncnntcca	agggggggnc	ggcccccaat	ccccccaacc	ntnaattnan	tttancccn	660
ccccngggcc	cggcctttta	cnancntcnn	nnacngggna	aaaccnnngc	tttncccaac	720

nnaatccncc t

731

<210> 20  
 <211> 754  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(754)  
 <223> n = A,T,C or G

<400> 20  
 tttttttttt tttttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc 60  
 caaccccctc ntccaaatnn ccntttccgg gnggggggtc caaacccaan ttanntttgg 120  
 annttaaatt aaatnttntt tggnggnna anccnaatgt nangaaagtt naaccanta 180  
 tnancttnaa tncctggaaa cngtngntt caaaaaatnt ttaaccctta antccctccg 240  
 aaatngttna nggaaaaccc aanttctcnt aaggttggtt gaaggntnaa tnaaaanccc 300  
 nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa 360  
 gggnancccc gggtantnaa tcccccnnc cccaattata ccganttttt ttngaattgg 420  
 ganccncggy gaattaacgy gggnnttccc tnttgggggg cnggnncccc ccccntcggy 480  
 gggtngggnc aggnncnaat tggttaaggg tccgaaaaat ccctccnaga aaaaaanctc 540  
 ccaggntgag nntnggggtt ncccccccc cangggccct ctcgnaaggt tgggggttgg 600  
 ggggctctgg attttnttcc cctnttnc tcccccccc ccnggganag aggttngngt 660  
 tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga 720  
 agtccttgn agggntaaan ggccccctnn cggy 754

<210> 21  
 <211> 755  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(755)  
 <223> n = A,T,C or G

<400> 21  
 atcancat gacccnaac nngggacnc tcanccgnc nnncnaccnc cggccnatca 60  
 nngtnagnnc actncnnttn natcacnccc cncnactac gcccnananc cnacgcncta 120  
 nncanattcc actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn 180  
 ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn 240  
 nncnncanac gatcttctn anccgattac ccntncccc tanccctcc cccccaacna 300  
 cgaaggcnct ggncnaagg nngcgnccc ccgctagntc ccnncaagt cncnnccta 360  
 aactcancn nattaacgc ttcttgagta tctctcccga aatctcacc tactcaactc 420  
 aaaaanacn gatacaaat aatncaagcc tgnttatnac actntgactg ggtctctatt 480  
 ttagnngtcc ntnaanctc ctaatacttc cagtctncc tcnccaattt ccnaanggt 540  
 ctttngaca gcatntttt gttccnntt gggtctcttan ngaattgccc ttctnngaac 600  
 gggctctct tttcttcgg ttanctggn ttcnccggc cagttattat ttccntttt 660  
 aaattctnc cntttanttt tggctttna aacccccggc cttgaaaacg gccccctggt 720  
 aaaaggttgt ttganaaaa ttttgtttt gttcc 755

<210> 22  
 <211> 849  
 <212> DNA  
 <213> Homo sapien  
  
 <220>

<221> misc\_feature  
 <222> (1)...(849)  
 <223> n = A,T,C or G

<400> 22  
 tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt 60  
 acgctnngan taangcgacc cganttctag ganncnccct aaaatcanac tgtgaagatn 120  
 atcctgnnna cggaanggtc accggnngat nntgctaggg tgncnctcc cannncttn 180  
 cataactcng nggccctgcc caccaccttc ggccggccng ngncggggcc cgggtcattn 240  
 gnnttaaccn cactnngcna ncggtttccn nccccnncng acccnggcga tccggggtn 300  
 tctgtcttcc cctgnagncn anaaantggg ccnccggncce ctttaccctt nnacaagcca 360  
 cngcctteta nccnngccc cccctccant nngggggact gccnanngct ccgttncnng 420  
 nnaccnccnn gggtnccctg gttgtcgant cnaccgnang ccanggattc cnaaggaagg 480  
 tgcgttnttg gccctaccc ttcgctnccg nncacccttc ccgacnanga nccgtcccgc 540  
 cncnccgng cctcncctcg caacaccgc nctcntngt ncggnnnccc cccacccgc 600  
 nccctcncn ngncgnancn ctccnccncc gtctcannca ccaccccgcc ccgccaggcc 660  
 ntcancnccn ggngacnng nagnccnttc gcncgcgcn gcgnccncc cgcncngaa 720  
 ctncntcngg ccantnccgc tcaancnna cnaaacgccg ctgcgcggcc cgnagcgncc 780  
 nccctcncga gtccctccgn ctcccnacc angnttccn cgaggacacn nnaccnccgc 840  
 nncangcgg 849

<210> 23  
 <211> 872  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(872)  
 <223> n = A,T,C or G

<400> 23  
 gcgcaaaact tacttcgctc gnactcgtgc gcctcgtcnc tcttttcctc cgcaaccatg 60  
 tctgacnanc ccgattnggc ngatatchan aagntcganc agtccaaact gantaacaca 120  
 cacacnanc aganaaatcc nctgccttcc anagtanacn attgaacnng agaaccangc 180  
 nggcgaatcg taatnaggcg tgcgcgcgcca atntgtcncc gtttatttnn ccagcncnc 240  
 ctncnacc ccacntcttc nagctgtcnn acccctngtn cgnaccccc naggtcggga 300  
 tccgggtttnn nntgaccgng cnnccctcc cccntccat nacganccn ccgcaccacc 360  
 nanngcncgc nccccgnnct ctccgcncn ctgtccttnn cccctgtngc ctggcncngn 420  
 accgcattga cctcgcnn ctncnngaaa ncgnanacgt ccgggttggn annancgctg 480  
 tgggnngcg tctgcncgc gttccttcn ncncttcca ccatcttct tacngggct 540  
 ccncgcctc tcnnncacn cctgggacgc tntcctntgc ccccttnac tccccctt 600  
 cgcgtgnc cgccccacc ntcatttnca nacgntcttc acaannncc ggntnctcc 660  
 cnancngncn gtcancnag ggaaggngg ggncnctg nttgacgttg ngngangtc 720  
 cgaanantcc tcnccntcan cctaccct cgggcggnct ctngttnc aacttancaa 780  
 ntctcccccg ngngcncntc tcagcctcnc cncnccnct ctctgcantg tntctgctc 840  
 tnaccnntac gantntcgn cncctctt cc 872

<210> 24  
 <211> 815  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(815)  
 <223> n = A,T,C or G

&lt;400&gt; 24

gcatgcaagc	ttgagtattc	tatagngtca	cctaaatanc	ttggcntaat	catggtcnta	60
nctgncttcc	tgtgtcaa	gtatacna	tanatatgaa	tctnatntga	caaganngta	120
tcntncatta	gtaacaantg	tnntgtccat	cctgtcngan	canattccca	tnnattncgn	180
cgcatcncn	gncantatn	taatngggaa	ntcnnntnnn	ncaccnncat	ctatcntncc	240
gcncctgac	tggnagagat	ggatnanttc	tnntntgacc	nacatgttca	tcttggattn	300
aanancccc	cgcngnccac	cggttngnng	cnagccnntc	ccaagacctc	ctgtggaggt	360
aacctgcgtc	aganncatca	aacntgggaa	accgcgnncc	angtnnaagt	ngnnncanan	420
gatcccgctc	aggnttnacc	atcccttcnc	agcgccccct	ttngtgcctt	anagnnagc	480
gtgtccnanc	cnetcaacat	ganacgcgcc	agnccanccg	caattnggca	caatgtcgnc	540
gaacccccta	gggggantna	tncaaanccc	caggattgtc	cncncangaa	atcccnanc	600
ccnccctac	ccncttttg	gacngtgacc	aantcccgga	gtncagctcc	ggcngnctc	660
ccccaccggt	nnccntgggg	gggtgaanct	cngnntcanc	cngncgaggn	ntcgnaagga	720
accggnccctn	ggncgaanng	ancnntcnga	agngccnct	cgtataaccc	cccctcncca	780
ncnancngnt	agntcccccc	cngggtnccg	aangg			815

&lt;210&gt; 25

&lt;211&gt; 775

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(775)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 25

ccgagatgtc	tcgctccgtg	gccttagctg	tgctcgcgct	actctctctt	tctggcctgg	60
aggctatcca	gcgtactcca	aagattcagg	tttactcacg	tcattccagca	gagaatggaa	120
agtcaaattt	cctgaattgc	tatgtgtctg	ggtttcatcc	atccgacatt	gaanttgcct	180
tactgaagaa	tgganagaga	attgaaaaag	tgagcattc	agacttgtct	ttcagcaagg	240
actggtcttt	ctatctcntg	tactacactg	aattcacccc	cactgaaaaa	gatgagtatg	300
cctgccgtgt	gaaccatgtg	actttgtcac	agcccaagat	agttaagtgg	gatcgagaca	360
tgtaagcagn	cnncatggaa	gtttgaagat	gccgcatttg	gattggatga	attccaaatt	420
ctgcttgctt	gcntttta	antgatatgc	ntatacacc	taccctttat	gncccaaat	480
tgtaggggtt	acatnantgt	tcnctngga	catgatcttc	ctttataant	ccnccnttcg	540
aattgcccgt	cncccngttn	ngaattgttc	cnnaaccacg	gttggtcccc	ccaggtcncc	600
tcttacggaa	gggcctgggc	cnctttncaa	ggttggggga	accnaaaatt	tcncttntgc	660
cncccncca	cnntcttgng	nnncantttt	ggaacccttc	cnattccctt	tggcctcnna	720
nccttnncta	anaaaacttn	aaancgtngc	naaanntttn	acttcccccc	ttacc	775

&lt;210&gt; 26

&lt;211&gt; 820

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(820)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 26

anattantac	agtgtaatct	tttccagag	gtgtgtanag	ggaacggggc	ctagaggcat	60
cccanagata	ncttatanca	acagtgtctt	gaccaagagc	tgctgggcac	atttcctgca	120
gaaaagggtg	cggtccccat	cactcctcct	ctcccatagc	catcccagag	gggtgagtag	180
ccatcangcc	ttcggtggga	gggagtcang	gaaacaacan	accacagagc	anacagacca	240
ntgatgacca	tgggcgggag	cgagcctctt	ccctgnaccg	gggtggcana	nganagccta	300
nctgaggggt	cacactataa	acgttaacga	ccnagatnan	cacctgcttc	aagtgcaccc	360

ttcctacctg	acnaccagng	accnnnaact	gngcctggg	gacagcncctg	ggancageta	420
acnnagcact	cacctgcccc	cccatggcgg	tncgntcccc	tggtcctgnc	aagggaagct	480
ccctgttgga	attncgggga	naccaaggga	nccccctcct	ccanctgtga	aggaaaaann	540
gatggaattt	tncccttccg	gcnntcccc	tcttcttta	cacgccccct	mntactcntc	600
tccctctntt	ntcctgncnc	acttttnacc	cnnnatttc	ccttnattga	tcggannctn	660
ganattccac	tnncgcctnc	cntcnatcng	naanacnaaa	nactntctna	cccggggat	720
gggnncctcg	ntcatcctct	ctttttcnc	accnccnntt	ctttgcctct	ccttngatca	780
tccaacntc	gntggcctn	ccccccnnn	tcctttnc			820

&lt;210&gt; 27

&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(818)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 27

tctgggtgat	ggcctcttcc	tcctcagga	cctctgactg	ctctgggcca	aagaatctct	60
tgtttcttct	ccgagcccca	ggcagcgggtg	attcagccct	gccaacctg	attctgatga	120
ctgcggtatgc	tgtgacggac	ccaaggggga	aatagggtcc	cagggtccag	ggaggggcgc	180
ctgctgagca	cttccgcgcc	tcaccctgcc	cagccctgc	catgagctct	gggtgggtc	240
tccgcctcca	gggttctgct	cttccangca	ngccancaag	tggcgctggg	ccacactggc	300
ttcttctgc	ccntccctg	gctctganc	tctgtcttcc	tgctctgtgc	angcnccttg	360
gatctcagtt	tcctcncctc	anngaactct	gtttctgann	tcttcantta	actntgantt	420
tatnaccnan	tggnctgtnc	tgtcnnactt	taatgggcn	gaccggctaa	tcctccctc	480
ntcccttcc	antcnnnna	accngcttnc	cntcncctcc	ccntancccg	ccngggaanc	540
ctcctttgcc	ctnaccangg	gcnnnaccg	ccntnnctn	ggggggcng	gtnnctncnc	600
ctgntncccc	cncctcncnt	tnccctgtcc	cnnncncgn	nngcannttc	ncngtccenn	660
tnnctcttcn	ngntcgnaa	ngntcncntn	tnnnnngncn	ngntnntncn	tcctctcnc	720
cnnntgnang	tnntnnnnnc	ncngnncccc	nnnnnnnnn	nggnntnnn	tctncncngc	780
cccncccc	ngnattaagg	cctcncntct	ccggcnc			818

&lt;210&gt; 28

&lt;211&gt; 731

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(731)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 28

aggaaggcg	gaggatatt	gtangggatt	gagggatagg	agnataangg	gggaggtgtg	60
tccaacatg	anggtgnngt	tctcttttga	angagggttg	ngttttann	ccnggtgggt	120
gattnaaccc	cattgtatgg	agnnaaaggn	tttnagggat	ttttcggtc	ttatcagtat	180
ntanattcct	gtnaatcgga	aatnatntt	tcnnccgaa	aatnttgctc	ccatccgnaa	240
attncctccg	ggtagtgc	nttnggggn	cngccangtt	tcccaggctg	ctanaatcgt	300
actaaagntt	naagtgggan	tncaaatgaa	aacctnncac	agagnatccn	tacccgactg	360
tnnntnccct	tcgccctntg	actctgcng	agcccaatac	ccnngngnat	gtcncncngn	420
nnngcgnenc	tgaaannnnc	tcngggctnn	gancatcang	gggtttcgca	tcaaaagcnn	480
cgtttcncat	naaggcactt	tngcctcatc	caaccnctng	ccctcnncca	tttngccgtc	540
nggttncct	acgctnntng	cncctnnntn	ganattttnc	ccgcctnggg	naancctcct	600
gnaatgggta	gggncttntc	ttttnaccnn	gnggtntact	aatcnnctnc	acgctnctt	660
tctcnacccc	ccccctttt	caatcccanc	ggcnaatggg	gtctccccnn	cgangggggg	720

nnncccannc c

731

<210> 29  
 <211> 822  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(822)  
 <223> n = A,T,C or G

&lt;400&gt; 29

actagtcag	tgtggtgaa	ttccattgtg	ttggggncnc	ttctatgant	antnttagat	60
cgctcanacc	tcacancctc	ccnacnangc	ctataangaa	nannaataga	nctgtncnnt	120
atntntacnc	tcatanncct	cnnnacccac	tccctcttaa	cccntactgt	gcctatngcn	180
tnnctantct	ntgccgcctn	cnanccaccn	gtggggccnac	cncnngnatt	ctcnatctcc	240
tcnccatntn	gcctananta	ngtncatacc	ctatacctac	nccaatgcta	nnnctaancn	300
tccatnantt	annntaacta	ccactgacnt	ngactttcnc	atnanctcct	aatttgaatc	360
tactctgact	cccacngcct	annnattagc	ancntccccc	nacnatntct	caaccaaadc	420
ntcaacaacc	tatctantctg	ttcnccaacc	nttnccctccg	atccccnnac	aacccccctc	480
ccaaataccc	nccacctgac	ncctaaccn	caccatcccg	gcaagccnan	ggncatttan	540
ccactggaat	cacnatngga	naaaaaaaaa	ccnaactctc	tancncnnat	ctccctaana	600
aatnctcctn	naatttactn	ncantnccat	caancccaen	tgaaacnnaa	cccctgtttt	660
tanatccctt	ctttcgaaaa	ccnacccttt	annncccaac	ctttngggcc	cccccnctnc	720
ccnaatgaag	gncncccaat	cnangaaacg	nccntgaaaa	ancnaggcna	anannntccg	780
canatcctat	cccttanttn	ggggncctt	nccengggcc	cc		822

<210> 30  
 <211> 787  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(787)  
 <223> n = A,T,C or G

&lt;400&gt; 30

cggccgcctg	ctctggcaca	tgccctctga	atggcatcaa	aagtgatgga	ctgccattg	60
ctagagaaga	ccttctctcc	tactgtcatt	atggagccct	gcagactgag	ggctcccctt	120
gtctgcagga	tttcatgtct	gaagtctgtg	agtgtggctt	ggagctcctc	atctacatna	180
gctggaagcc	ctggagggcc	tctctcgcca	gcctccccct	tctctccacg	ctctccangg	240
acaccagggg	ctccaggcag	cccattatc	ccagnangac	atgggtgttc	tccacgggga	300
cccatggggc	ctgnaaggcc	agggctctct	ttgacaccat	ctctcccgtc	ctgcctggca	360
ggccgtggga	tccactantt	ctanaacggn	gcgccaccncg	gtgggagctc	cagcttttgt	420
tcccnttaat	gaagggtaat	tgcnccgttg	gcgtaatcat	nggtcanaac	tnnttctgt	480
gtgaaattgt	ttntccccctc	ncnattccnc	ncnacatacn	aacccggaan	cataaagtgt	540
taaagcctgg	gggtngcctn	ngaataa	tnaactcaat	taattgcgtt	ggctcatggc	600
ccgctttccn	ttcnggaaaa	ctgtctctcc	ctgcnttntt	gaatcggcca	cccccnngg	660
aaaagcgtt	tgcnttttng	ggggntcctt	ccncttcccc	cctcnctaan	ccctncgcct	720
cggctgttnc	nggtngcggg	gaangggnat	nnnctccnc	naagggggng	agnnngntat	780
ccccaaa						787

<210> 31  
 <211> 799  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(799)  
 <223> n = A,T,C or G

<400> 31

tttttttttt	tttttttggc	gatgctactg	tttaattgca	ggaggtgggg	gtgtgtgtac	60
catgtaccag	ggctattaga	agcaagaagg	aaggagggag	ggcagagcgc	cctgctgagc	120
aacaaaggac	tcctgcagcc	ttctctgtct	gtctcttggc	gcaggcacat	ggggaggcct	180
cccgagggt	gggggccacc	agtccagggg	tgggagcact	acanggggtg	ggagtgggtg	240
gtggctggtn	cnaatggcct	gncacanatc	cctacgattc	ttgacacctg	gatttcacca	300
ggggaccttc	tggtctccca	nggnaacttc	ntnnatctcn	aaagaacaca	actgtttctt	360
cngcanttct	ggctgttcat	ggaaagcaca	ggtgtccnat	ttnggctggg	acttggtaca	420
tatggttccg	gcccacctct	cccntcnaa	aagtaattca	ccccccccc	ccntctnttg	480
cctgggccct	taantaccca	caccggaact	canttantta	ttcatcttng	gntgggcttg	540
ntnatcnccn	cetgaangcg	ccaagttgaa	aggccacgcc	gthcccnctc	cccatagnan	600
nttttntnt	canctaatac	ccccccnggc	aacnatccaa	tcccccccn	tggggggccc	660
agcccanggc	ccccgntcgc	ggnnnccngn	cncgnantcc	ccagntcttc	ccantcngnc	720
ccnnngcncc	cccgcacgca	gaacanaagg	ntngagccnc	cgcannnnnn	nggtnnccna	780
ctcgcccccc	ccnnccngg					799

<210> 32  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 32

tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tttttncnag	ggcagggtta	ttgacaacct	cncgggacac	aancaggctg	gggacaggac	120
ggcaacaggc	tccggcgggc	gcggcgggcg	ccctacctgc	ggtaccaa	ntgcagcctc	180
cgctcccgc	tgatnttcc	ctgcagctgc	aggatgccnt	aaaacagggc	ctcgccntn	240
ggtgggcacc	ctgggatttn	aatttccacg	ggcacaatgc	ggtcgcancc	cctcaccacc	300
nattaggaat	agtggtnnta	cccnccnccg	ttggcncact	ccccntggaa	accacttntc	360
gcggctccgc	catctggtct	taaaccttgc	aaacnctggg	gccctctttt	tggttantnt	420
nccngccaca	atcatnactc	agactggcnc	gggctggccc	caaaaaancn	ccccaaaacc	480
ggncatgtc	ttnnccgggt	tgctgcnatn	tncatcacct	ccccggcnca	ncaggncaac	540
ccaaaagtgc	ttngggcccn	caaaaaanct	ccggggggnc	ccagtttcaa	caaagtcac	600
ccccttggcc	cccaaatact	ccccccgntt	ncgtgggttg	ggaacccacg	cctctnnctt	660
tggnnggcaa	gntggntccc	ccttcgggcc	cccgggtggc	ccnctctaa	ngaaaacncc	720
ntcctnnnca	ccatcccccc	nngnnacgnc	tancaangna	tccctttttt	tanaaacggg	780
ccccccnccg						799

<210> 33  
 <211> 793  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(793)  
 <223> n = A,T,C or G



&lt;400&gt; 33

gacagaacat	ggttgatggt	ggagcacctt	tctatacgac	ttacaggaca	gcagatggg	60
aattcatggc	tggttgagca	atanaacccc	agttctacga	gctgctgac	aaaggacttg	120
gactaaagtc	tgatgaactt	cccaatcaga	tgagcatgga	tgattggcca	gaaatgaana	180
agaagtttgc	agatgtat	gcaaagaaga	cgaaggcaga	gtggtgtcaa	atctttgacg	240
gcacagatgc	ctgtgtgact	ccggttctga	cttttgagga	ggttggtcat	catgatcaca	300
acaangaacg	gggctcgttt	atcaccantg	aggagcagga	cgtgagcccc	cgccctgcac	360
ctctgctgtt	aaacacccca	gccatccctt	ctttcaaaag	ggatccacta	cttctagagc	420
ggncgccacc	gcggtggagc	tccagctttt	gttcccttta	gtgaggggta	attgcgcgct	480
tggcgtaatc	atggtcatan	ctgtttcctg	tgtgaaattg	ttatccgctc	acaattccac	540
acaacatacg	anccggaagc	atnaaatttt	aaagcctggg	ggtngcctaa	tgantgaact	600
nactcacatt	aattggcttt	gcgctcactg	cccgcctttc	agtccggaaa	acctgtcctt	660
gccagctgcc	nttaatgaat	cnggccaccc	cccggggaaa	aggcngtttg	cttnttgggg	720
cgcncctccc	gctttctcgc	ttcctgaant	ccttcccccc	ggtctttcgg	cttgccggcna	780
acggtatcna	cct					793

&lt;210&gt; 34

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(756)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 34

gccgcgaccg	gcatgtacga	gcaactcaag	ggcgagtggg	accgtaaaa	ccccaatctt	60
ancaagtgcg	gggaanagct	gggtcgactc	aagctagttc	ttctggagct	caacttcttg	120
ccaaccacag	ggaccaagct	gaccaaacag	cagctaattc	tggcccgtga	catactggag	180
atcgggggccc	aatggagcat	cctacgcaan	gacatccct	ccttcgagcg	ctacatggcc	240
cagctcaaat	gctactactt	tgattacaan	gagcagctcc	ccgagtcagc	ctatatgcac	300
cagctcttgg	gcctcaacct	cctcttcctg	ctgtcccaga	accgggtggc	tgantnccac	360
acgganttgg	ancggctgcc	tgcccaanga	catacanacc	aatgtctaca	tcnaccacca	420
gtgtcctgga	gcaatactga	tgganggcag	ctaccncaa	gtnttcctgg	ccnagggtaa	480
catccccgcg	cgagagctac	accttcttca	ttgacatcct	gctcgacact	atcagggatg	540
aaaatcgcn	ggttgctcca	gaaaggctnc	aanaanatcc	ttttcncctga	aggcccccg	600
atnncctagt	nctagaatcg	gcccgccatc	gcggtgganc	ctccaacctt	tcgttnccct	660
ttactgaggg	ttnattgccg	cccttgccgt	tatcatggtc	acnccngttn	cctgtgttga	720
aattnttaac	ccccacaa	tccacgcna	cattng			756

&lt;210&gt; 35

&lt;211&gt; 834

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(834)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 35

ggggatctct	anactnacct	gnatgcatgg	ttgtcgggtg	ggtcgctgtc	gatgaanatg	60
aacaggatct	tgcccttgaa	gctctcggct	gctgtnttta	agttgctcag	tctgccgtca	120
tagtcagaca	cncctcttgg	caaaaaacan	caggatntga	gtcttgattt	cacctccaat	180
aatcttcngg	gctgtctgct	cggtgaactc	gatgacnang	ggcagctggg	tgtgtntgat	240
aaantccanc	angttctcct	tggtgacctc	cccttcaaag	ttgttcgggc	cttcatcaaa	300
cttctnnaan	angannanc	canccttgtc	gagctgggat	ttgganaaca	cgctcactgtt	360

```

ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt      420
ggcncaaatc cgactcccn tccttgaaag aagccnatca cacccccctc cctggactcc      480
nncaangaact ctncgcgtnc cccntccnng cagggttggg ggcannccgg gcccntgcgc      540
ttcttcagcc agttcacnat nttcatcagc cctctgcca gctgtntat tccttggggg      600
ggaanccgtc tctcccttcc tgaannaact ttgaccgtng gaatagccgc gentcncnt      660
acntnctggg ccgggttcaa antccctccn ttgncnntcn cctcgggcca ttctggattt      720
nccnaacttt ttcttcccc cccccnccg ngtttggnnt tttcatnggg ccccaactct      780
gctnttgccc antccctgg gggcntntan cccccctnt ggtcccntng ggcc      834

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```

<210> 36
<211> 814
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(814)
<223> n = A,T,C or G

```

```

<400> 36
cggncgcttt ccngccgcgc cccgtttcca tgacnaaggc tcccttcang ttaaatacnn      60
cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgcca      120
naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggctctctc accccctgta      180
ggaaaggcct gccttgtaag acaccacaat ncggctgaat ctnaagtctt gtgttttact      240
aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgccaccg cagcctggca      300
ctaaaacanc ccagcgtca cttctgcttg ganaaatatt ctttgcctt ttggacatca      360
ggcttgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc      420
antganctgg aaggcctgaa ncttagtctc caaaagtctc ngcccacaag accggccacc      480
aggggangtc nttncagtg gatctgccaa anantaccn tatcatcnn gaataaaaag      540
gccctgaac ganatgcttc cancancctt taagaccat aatcctngaa ccatgggccc      600
cttcgggtct gatecnaaag gaatgttctt ggggtccant cctcctttg ttncttacgt      660
tgnttggaac cntgctngn atnaccaan tganatcccc ngaagcacc tnccttggc      720
atttganctt cntaaattct ctgcctacn nctgaaagca cnattccctn ggcncnaaan      780
gngaactca agaaggtctn ngaaaaacca cncn      814

```

```

<210> 37
<211> 760
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(760)
<223> n = A,T,C or G

```

```

<400> 37
gcattgctgt cttcctcaaa gttgttcttg ttgccataac aaccaccata ggtaaagcgg      60
gcgcagtggt cgctgaagg gttgtagtac cagcgcggga tgctctcctt gcagagtcct      120
gtgtctggca ggtccacgca atgccctttg tcaactggga aatggatgag ctggagctcg      180
tcnaanccac tctgtatatt ttacangca gcctcctcag aagcctccgg gcagttgggg      240
gtgtcgtcac actccactaa actgtgatn cancagccca ttgtgcagc ggaactgggt      300
gggctgacag gtgccagaac aactggatn ggcctttcca tggaagggcc tgggggaaat      360
cncctnancc caaactgcct ctcaaaggcc accttgaca ccccgacagg ctagaaatgc      420
actcttcttc ccaaaggtag ttgttcttgt tgccaagca ncctccanca aaccaaanc      480
ttgcaaaatc tgctcctgg gggctcatnn taccanggtt ggggaaanaa acccgcnngn      540
ganccnctt gtttgaatgc naaggnaata atcctcctgt cttgcttggg tggaaanagca      600
caattgaact gttaacnttg ggccnggttc cctnggggtg gtctgaaact aatcacgctc      660
actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnttt      720

```

ctcctctncc ctaaaaatcg tnttcccccc cctangcg

760

<210> 38  
 <211> 724  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(724)  
 <223> n = A,T,C or G

<400> 38  
 tttttttttt tttttttttt tttttttttt tttttaaaaa cccctccat tgaatgaaaa 60  
 cttcnnaaat tgtccaaccc cctcnnccaa atnncattt ccgggggggg gttccaaacc 120  
 caaattaatt ttgganttta aattaaatnt tnatnngggg aanaanccaa atgtnaagaa 180  
 aatttaaccc attatnaact taaatncctn gaaaccctg gnttccaaaa atttttaacc 240  
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt 300  
 ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt 360  
 tcctnttaan cntnggtaac tcccngtaat gaannnccct aanccaatta aaccgaattt 420  
 tttttgaatt ggaaattccn ngggaattna ccgggggttt tcccntttgg gggccatncc 480  
 cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana 540  
 aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg 600  
 tttntggggg ccngggantt cnttccccc ttnccncccc cccccnggt aaanggttat 660  
 ngnttttgtt ttttggcccc cttnanggac cttccggatn gaaattaaat ccccggnccg 720  
 gccg 724

<210> 39  
 <211> 751  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 39  
 tttttttttt ttttcttttg ctcacattta atttttattt tgattttttt taatgctgca 60  
 caacacaata tttatttcat ttgtttcttt tatttcattt tatttgttg ctgctgctgt 120  
 tttatttatt tttactgaaa gtgagaggga acttttgtgg ccttttttcc tttttctgta 180  
 ggccgcctta agctttctaa atttggaaaca tctaagcaag ctgaanggaa aaggggggtt 240  
 cgcaaaatca ctcgggggaa nggaaagggt gctttgttaa tcatgcccta tgggtgggtga 300  
 ttaactgctt gtacaattac ntttactttt taattaattg tgctnaangc ttaattana 360  
 cttgggggtt ccttccccc accaaccnccn ctgacaaaaa gtgccngccc tcaaatnatg 420  
 tcccgcnnt cnttgaaaca cacngcngaa ngttctcatt ntccccnccn caggtnaaaa 480  
 tgaagggtta ccatntttta cncacctcc acntggcnnn gcctgaatcc tcnaaaancn 540  
 ccccaancn aattnctnng ccccggtcnc gcntnngtcc cncccgggct ccgggaantn 600  
 caccgccnga anncnntnnc naacnaaatt ccgaaaatat tcccnntcnc tcaattcccc 660  
 cnnagactnt cctcnncnan cncaattttc tttntntcac gaacnccnnc cnnaaatgn 720  
 nnnnccctc cncnngtcen naatcnccan c 751

<210> 40  
 <211> 753  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(753)  
 <223> n = A,T,C or G

<400> 40

gtgggtatttt	ctgtaagatc	aggtgttcct	ccctcgtagg	ttagaggaa	acaccctcat	60
agatgaaaac	ccccccgaga	cagcagcact	gcaactgcc	agcagccggg	gtaggagggg	120
cgccctatgc	acagctgggc	ccttgagaca	gcagggttc	gatgtcaggc	tcgatgtcaa	180
tggctctgaa	gcggcggctg	tacctgcgta	ggggcacacc	gtcagggccc	accaggaact	240
tctcaaagtt	ccaggcaacn	tcgttgcgac	acaccggaga	ccaggtgatn	agcttggggg	300
cggtcataan	cgcggtggcg	tcgtcgctgg	gagctggcag	ggcctcccgc	aggaaggcna	360
ataaaagggtg	cgcccccgca	ccgttcanc	cgcaacttctc	naanaccatg	angttgggct	420
cnaaccacc	accannccgg	acttccttga	nggaattccc	aaatctcttc	gntcttgggc	480
ttctnctgat	gccctancg	gttgcccnng	atgccaanca	nccccaancc	ccggggctct	540
aaanaccn	cctcctcmtt	tcactctggg	tntntcccc	ggacctggg	tcctctcaag	600
gganccata	tctcnaccan	tactcacnt	nccccccnt	gnnaccan	cttctannng	660
ttccncccg	ncctctggcc	cntcaaan	gcttnca	cctgggtctg	ccttcccccc	720
tnccctatct	gnacccn	ttgtctcan	tnt			753

<210> 41  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 41

actatatcca	tcacaacaga	catgcttcat	cccatagact	tcttgacata	gcttcaaagt	60
agtgaaccca	tccttgattt	atatacatat	atgttctcag	tattttggga	gcctttccac	120
ttctttaaac	cttggttcatt	atgaacactg	aaaataggaa	tttgtaaga	gttaaaaagt	180
tatagcttgt	ttacgtagta	agtttttgaa	gtctacattc	aatccagaca	cttagttgag	240
tgttaaactg	tgatttttaa	aaaatatcat	ttgagaatat	tctttcagag	gtattttcat	300
ttttactttt	tgattaattg	tgttttatat	attagggtag	t		341

<210> 42  
 <211> 101  
 <212> DNA  
 <213> Homo sapien

<400> 42

acttactgaa	tttagttctg	tgctcttcct	tatttagtgt	tgtatcataa	atactttgat	60
gtttcaaaca	ttctaaataa	ataattttca	gtggcttcat	a		101

<210> 43  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 43

acatctttgt	tacagtctaa	gatgtgttct	taaatcacca	ttccttcctg	gtcctcaccc	60
tcagggtgg	tctcacactg	taattagagc	tattgaggag	tctttacagc	aaattaagat	120
tcagatgcct	tgctaagtct	agagttctag	agttatgttt	cagaaagtct	aagaaaccca	180
cctcttgaga	ggtcagtaaa	gaggacttaa	tatttcatat	ctacaaaatg	accacaggat	240
tggatacaga	acgagagtta	tcctggataa	ctcagagctg	agtacctgcc	cggggggccgc	300
tcgaa						305

<210> 44  
 <211> 852  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(852)  
 <223> n = A,T,C or G

<400> 44

acataaatat	cagagaaaag	tagtctttga	aatatttacg	tccaggagtt	ctttgtttct	60
gattatttgg	tgtgtgtttt	ggtttgtgtc	caaagtattg	gcagcttcag	ttttcatttt	120
ctctccatcc	tcgggcattc	ttcccaaatt	tatataccag	tcttcgtcca	tccacacgct	180
ccagaatttc	tctttttag	taatatctca	tagctcggct	gagcttttca	taggtcatgc	240
tgctgttgtt	cttcttttta	ccccatagct	gagccactgc	ctctgatttc	aagaacctga	300
agacgccctc	agatcggctc	tcccatttta	ttaatcctgg	gttcttgcct	gggttcaaga	360
ggatgtcgcg	gatgaattcc	cataagttag	tccctctcgg	gttcttgcct	ttggtgtggc	420
acttggcagg	ggggctctgc	tcctttttca	tatcagggtga	ctctgcaaca	ggaaggtgac	480
tggtggttgt	catggagatc	tgagcccggc	agaaagtttt	gctgtccaac	aaatctactg	540
tgctaccata	gttgggtgtca	tataaatagt	tctngtcttt	ccagggtgttc	atgatggaag	600
gctcagtttg	ttcagtcttg	acaatgacat	tgtgtgtgga	ctggaacagg	tcactactgc	660
actggccggt	ccacttcaga	tgctgcaagt	tgctgtagag	gagntgcccc	gccgtccctg	720
ccgcccgggt	gaactcctgc	aaactcatgc	tgcaaagggt	ctcgccgttg	atgtcgaaact	780
cntgaaaagg	gatacaattg	gcattccagct	ggttggtgtc	caggagggtga	tggaagccact	840
cccacacctg	gt					852

<210> 45  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

<400> 45

acaacagacc	cttgctcgct	aacgacctca	tgctcatcaa	gttggacgaa	tccgtgtccg	60
agtctgacac	catccggagc	atcagcattg	cttcgcagtg	ccctaccgcg	gggaactctt	120
gcctcgtttc	tggtctgggt	ctgctggcga	acggcagaat	gcctaccgtg	ctgcagtgcg	180
tgaacgtgtc	ggtggtgtct	gaggagggtc	gcagtaagct	ctatgacccg	ctgt	234

<210> 46  
 <211> 590  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(590)  
 <223> n = A,T,C or G

<400> 46

actttttatt	taaatgttta	taaggcagat	ctatgagaat	gatagaaaac	atggtgtgta	60
atttgatagc	aatatttttg	agattacaga	gttttagtaa	ttaccaatta	cacagttaaa	120
aagaagataa	tatattccaa	gcanatacaa	aatatcta	gaaagatcaa	ggcaggaaaa	180
tgantataac	taattgacaa	tggaataatca	attttaatgt	gaattgcaca	ttatccttta	240
aaagctttca	aaanaaanaa	ttattgcagt	ctanttaatt	caaacagtgt	ttaatgggtat	300
caggataaan	aactgaaggg	canaaagaat	taattttcac	ttcatgtaac	ncaccanant	360
ttacaatggc	ttaaatgcan	ggaaaaagca	gtggaagtag	ggaagtantc	aaggtctttc	420
tggtctctaa	tctgccttac	tctttgggtg	tggtcttgat	cctctggaga	cagctgccag	480
ggctcctggt	atatccacaa	tcccagcagc	aagatgaagg	gatgaaaaag	gacacatgct	540
gccttccttt	gaggagactt	catctcactg	gccaaactc	agtcacatgt		590

<210> 47  
 <211> 774

<212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(774)  
 <223> n = A,T,C or G

<400> 47

acaagggggc	ataatgaagg	agtggggana	gatttttaaag	aaggaaaaaa	aacgaggccc	60
tgaacagaat	tttcctgnac	aacggggcctt	caaaataatt	ttcttgggga	ggttcaagac	120
gcttcactgc	ttgaaactta	aatggatgtg	ggacanaatt	ttctgtaatg	accctgaggg	180
cattacagac	gggactctgg	gaggaaggat	aaacagaaag	gggacaaagg	ctaatacccaa	240
aacatcaaag	aaaggaagg	ggcgtcatac	ctcccagcct	acacagttct	ccagggtctct	300
cctcatccct	ggaggacgac	agtggaggaa	caactgacca	tgtccccagg	ctcctgtgtg	360
ctggctcctg	gtcttcagcc	cccagctctg	gaagcccacc	ctctgctgat	cctgcgtggc	420
ccacactcct	tgaacacaca	tccccaggtt	atattcctgg	acatggctga	acctcctatt	480
cctacttccg	agatgccttg	ctccctgcag	cctgtcaaaa	tcccactcac	cctccaaacc	540
acggcatggg	aagcctttct	gacttgccctg	attactccag	catcttgga	caatccctga	600
ttccccactc	cttagaggca	agataggggtg	gttaagagta	gggctggacc	acttgagacc	660
aggctgctgg	cttcaaattn	tggctcattt	acgagctatg	ggaccttggg	caagtnatct	720
tcacttctat	gggcntcatt	ttgttctacc	tgcaaaatgg	gggataataa	tagt	774

<210> 48  
 <211> 124  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(124)  
 <223> n = A,T,C or G

<400> 48

canaaattga	aattttataa	aaaggcattt	ttctcttata	tccataaaat	gatataattt	60
ttgcaantat	anaaatgtgt	cataaattat	aatgttcctt	aattacagct	caacgcaact	120
tggt						124

<210> 49  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 49

gccgatgcta	ctattttatt	gcaggagggtg	gggggtgtttt	tattattctc	tcaacagctt	60
tgtggctaca	ggtggtgtct	gactgcatna	aaaanttttt	tacgggtgat	tgcaaaaatt	120
ttagggcacc	catatcccaa	gcantgt				147

<210> 50  
 <211> 107  
 <212> DNA  
 <213> Homo sapien

<400> 50  
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatattattgc 60  
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt 107

<210> 51  
<211> 204  
<212> DNA  
<213> Homo sapien

<400> 51  
gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg 60  
cggaagaa aggcagagaa gtgacaccgt cagggggaaa tgaoagaaag gaaaatcaag 120  
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttgacca 180  
cctccctttt gggaccagca atgt 204

<210> 52  
<211> 491  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(491)  
<223> n = A,T,C or G

<400> 52  
acaaagataa catatatctt ataacaaaaa tttgatagtt ttaaagggtta gtattgtgta 60  
gggtattttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120  
ccatcagaca ggttttttaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa 180  
aaaacttctt gtatcaattt cttttgttca aaatgactga ctttaantatt tttaaatatt 240  
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtnc ctcagtccca 300  
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360  
atgcaacagt gtcttttctt tnccttttct tttttttttt ttacaggcac agaaactcat 420  
caattttatt tggataacaa agggctctcca aattatattg aaaaataaat ccaagttaat 480  
atcactcttg t 491

<210> 53  
<211> 484  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(484)  
<223> n = A,T,C or G

<400> 53  
acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60  
gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac 120  
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct 180  
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct 240  
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300  
agctttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttggt gcctctccct 360  
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncc 420  
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc 480  
cant 484

<210> 54

aatcagtgc tccaggattg gtccttggat ctggggg

97.

<210> 65  
 <211> 377  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(377)  
 <223> n = A,T,C or G

<400> 65  
 acaacaanaa ntcccttctt taggcactg atggaaacct ggaacccctt tttgatggca 60  
 gcatggcgctc ctaggccttg acacagcggc tggggtttgg gctntcccaa accgcacacc 120  
 ccaaccctgg tctacccaca nttctggcta tgggctgtct ctgccactga acatcagggt 180  
 tcggtcataa natgaaatcc caanggggac agagggtcagt agaggaagct caatgagaaa 240  
 ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg 300  
 tgggggtgaa ctacccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360  
 gggcgggagg agcatgt 377

<210> 66  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 66  
 acgcctttcc ctcagaattc agggaagaga ctgtcgctg ccttctctcg ttgttgctg 60  
 agaaccctg tgccccctcc caccatatcc accctcgctc catctttgaa ctcaaacacg 120  
 aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tccctcacct 180  
 tcctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt 240  
 ttatatattt tttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300  
 tggtt 305

<210> 67  
 <211> 385  
 <212> DNA  
 <213> Homo sapien

<400> 67  
 actacacaca ctccacttgc ctttgtgaga cactttgtcc cagcacttta ggaatgctga 60  
 ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcaggc ctgagagttc 120  
 cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc 180  
 tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg 240  
 ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgcttg 300  
 cctctcccag ggccccagcc tgcccacacc tgcttacagg gcactctcag atgcccatac 360  
 catagtttct gtgctagtgg accgt 385

<210> 68  
 <211> 73  
 <212> DNA  
 <213> Homo sapien

<400> 68  
 acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60  
 gtttttttaa tgg 73

<210> 69



<211> 536  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(536)  
 <223> n = A,T,C or G

<400> 69

actagtccag	tgtggtggaa	ttccattgtg	ttgggggctc	tcaccctcct	ctcctgcagc	60
tccagctttg	tgctctgcct	ctgaggagac	catggcccag	catctgagta	ccctgctgct	120
cctgctggcc	accctagctg	tggccctggc	ctggagcccc	aaggaggagg	ataggataat	180
cccggtggc	atctataacg	cagacctcaa	tgatgagtgg	gtacagcgtg	cccttcactt	240
cgccatcagc	gagtataaca	aggccaccaa	agatgactac	tacagacgtc	cgctgcgggt	300
actaagagcc	aggcaacaga	ccgttggggg	ggtgaattac	ttcttcgacg	tagaggtggg	360
ccgaaccata	tgtaccaagt	cccagcccaa	cttggacacc	tgtgccttcc	atgaacagcc	420
agaactgcag	aagaaacagt	tgtgctcttt	cgagatctac	gaagttccct	ggggagaaca	480
gaangtccct	gggtgaaatc	caggtgtcaa	gaaatcctan	ggatctgttg	ccaggc	536

<210> 70  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<400> 70

atgaccccta	acaggggccc	tctcagccct	cctaattgacc	tccggcctag	ccatgtgatt	60
tcacttccac	tccataacgc	tcctcatact	aggcctacta	accaacacac	taaccatata	120
ccaatgatgg	cgcgatgtaa	cacgagaaag	cacataccaa	ggccaccaca	caccacctgt	180
ccaaaaaggc	cttcgatacg	ggataatcct	atattattacc	tcagaagttt	ttttcttcgc	240
agggattttt	ctgagccttt	taccactcca	gcctagcccc	taccccccaa	ctaggaggggc	300
actggccccc	aacaggcatc	accccgctaa	atcccctaga	agtcccactc	ctaaacacat	360
ccgtattact	cgcatcagga	gtatcaatca	cctgagctca	ccatagtcta	atagaaaaca	420
accgaaacca	aattattcaa	agcactgctt	attacaattt	tactgggtct	ctatttt	477

<210> 71  
 <211> 533  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(533)  
 <223> n = A,T,C or G

<400> 71

agagctatag	gtacagtgtg	atctcagctt	tgcaaacaca	ttttctacat	agatagtact	60
aggattaat	agatatgtaa	agaaagaaat	cacaccatta	ataatggtaa	gattgggtta	120
tgtgatttta	gtggtatttt	tggcaccctt	atatatgttt	tccaaacttt	cagcagtgat	180
attattttca	taacttaaaa	agtgagtttg	aaaaagaaaa	tctccagcaa	gcatctcatt	240
taaataaagg	tttgtcatct	ttaaaaatac	agcaatatgt	gactttttta	aaaagctgtc	300
aaataggtgt	gaccctacta	ataattatta	gaaatacatt	taaaaacatc	gagtacctca	360
agtcagtttg	ccttgaaaaa	tatcaaatat	aactcttaga	gaaatgtaca	taaaagaatg	420
cttcgtaatt	ttggagtang	aggttccctc	ctcaattttg	tattttttaa	aagtacatgg	480
taaaaaaaa	aattcacaac	agtatataag	gctgtaaaaa	gaagaattct	gcc	533

<210> 72  
 <211> 511

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 54  
 actaaacctc gtgcttgtga actccatata gaaaacggtg ccatccctga acacggctgg 60  
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120  
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55  
 <211> 91  
 <212> DNA  
 <213> Homo sapien

<400> 55  
 acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc 60  
 gccctccagt ggatactcga gccaaagtgg t 91

<210> 56  
 <211> 133  
 <212> DNA  
 <213> Homo sapien

<400> 56  
 ggccgatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact 60  
 tggatttttg gtatctgtgg gttgggggga cgggccagga accaatacc catggatacc 120  
 aagggaacaac tgt 133

<210> 57  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 57  
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gcngtggcgc 60  
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120  
 tctcantggg ctggatncat gcagggt 147

<210> 58  
 <211> 198  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(198)  
 <223> n = A,T,C or G

<400> 58  
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc 60  
 tgattacata catttatcct ttaaaaaaga tgtaaatcctt aatttttatg ccatctatta 120  
 atttaccat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt 180  
 ttgacttcta agtttggt 198

actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat 480  
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtccccgt 537

<210> 75  
<211> 467  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(467)  
<223> n = A,T,C or G

<400> 75  
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc 60  
tgcatattac acgtacctcc tctgtctcct caagtagtgt ggtctatattt gccatcatca 120  
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg 180  
tggcacaagg aggccatctt ttctcatcg gttattgtcc ctagaagcgt cttctgagga 240  
tctagtggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta 300  
tcattattgt ataacggtt tcaaaccngt gggcacncag agaacctcac tctgtaataa 360  
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc 420  
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn 467

<210> 76  
<211> 400  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(400)  
<223> n = A,T,C or G

<400> 76  
aagctgacag cattogggcc gagatgtctc gctccgtggc cttagctgtg ctgcgctac 60  
tctctctttc tggcctggag gctatccagc gtactccaaa gattcagggt tactcacgtc 120  
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg ttcatccat 180  
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagt gagcattcag 240  
acttgtctt cagcaaggac tggcttttct atctcttgta ctacactgaa ttcaccccca 300  
ctgaaaaaga tgagtatgcc tggcgtgtga accatgtgac tttgtcacag cccaagatng 360  
ttnagtggga tcganacatg taagcagcan catgggaggt 400

<210> 77  
<211> 248  
<212> DNA  
<213> Homo sapien

<400> 77  
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60  
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgtgc 120  
caggcaactgt tcactctcagc ttttctgtcc ctttctccc ggcaagcgt tctgctgaaa 180  
gttcatatct ggagcctgat gtcttaacga ataaaggctc catgctccac ccgaaaaaaa 240  
aaaaaaaa 248

<210> 78  
<211> 201  
<212> DNA  
<213> Homo sapien

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(511)  
<223> n = A,T,C or G

<400> 72

tatttacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta	60
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa	120
aagccgcagg atgtctacac tatancaggc gctatctggg ttggctggag gagctgtgga	180
aaacatggan agattgggtgc tgganacgc cgtggctatt cctcattgtt attacanagt	240
gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca	300
cacatgagaa ctgaaatggc ccaaaccag aaagaaagcc caactagatc ctcagaanac	360
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgcccc gtctgttatg	420
atttctctcc attgcagcna naaaccggtt cttctaagca aacncagggtg atgatggcna	480
aaatacaccc cctcttgaag naccnggagg a	511

<210> 73  
<211> 499  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(499)  
<223> n = A,T,C or G

<400> 73

cagtgccagc actggtgccca gtaccagtac caataacagt gccagtgccca gtgccagcac	60
cagtgggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc	120
tggccttggt ggagctgggt ccagcaccag tggcagctct ggtgcctgtg gtttctccta	180
caagtgaagt tttagatatt gttaatcctg ccagtccttc tottcaagcc aggggtgcac	240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca	300
ctctgcatta aatctatttg ccatttctga aaaaaaaaaa aaaaaaaggc cggccgctcg	360
antctagagg gcccgtttaa acccgctgat cagcctcgac tgtgccttct anttgccagc	420
catctgttgt ttgccctcc cccgntgcct tccttgaccc tggaaagtgc cactccact	480
gtcctttcct aantaaat	499

<210> 74  
<211> 537  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(537)  
<223> n = A,T,C or G

<400> 74

tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat	60
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact	120
tccaggccca cggtcgaagt gaatttgaat actgcattta cagtgtagag taacacataa	180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga	240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag	300
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc	360
cagtttgctt gatataattg ttgatattaa gattcctgac ttatattttg aatgggttct	420

<400> 81  
 tttttttttg tatgccttcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt 60  
 ttcttctgta tctttctttt ctggggggtc ttcttggtc tgccctcca ttcccagcct 120  
 ctcatcccca tcttgcaatt ttgctagggt tggaggcgct ttcttggtag cccctcagag 180  
 actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct 232

<210> 82  
 <211> 383  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 82  
 aggcggggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc 60  
 agtaccagta ccaataacat gccagtgccg gtgccagcac cagtgggtggc ttcagtgcctg 120  
 gtgccagcct gaccgccact ctacacattg ggctcttcgc tggccttggg ggagctggtg 180  
 ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt 240  
 gttaatctg ccagtctttc tcttcaagcc aggtgtgcat ctcagaaacc tactcaacac 300  
 agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360  
 ccatttcaaa aaaaaaaaaa aaa 383

<210> 83  
 <211> 494  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(494)  
 <223> n = A,T,C or G

<400> 83  
 accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca 60  
 gggagatcga gtctatacgc tgaagaaatt tgaccgatg ggacaacaga cctgctcagc 120  
 ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa 180  
 acgcttcaag gtgctcatga cccagcaacc gcgccctgtc ctctgagggt ccttaaactg 240  
 atgtcttttc tgccacctgt taccctctgg agactccgta accaaaactct tcggactgtg 300  
 agccctgatg cctttttgcc agccatactc tttggcntcc agtctctcgt ggcgattgat 360  
 tatgcttggt tgaggcaatc atggtggcat caccatnaa gggaacacat ttganttttt 420  
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta 480  
 aaaaaaaaaa aaaa 494

<210> 84  
 <211> 380  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(380)  
 <223> n = A,T,C or G

<400> 84

&lt;400&gt; 78

actagtccag tgtggtggaa ttccattgtg ttgggcccac cacaatggct acctttaaca	60
tcaccagac cccgccctgc ccgtgcccac cgctgctgct aacgacagta tgatgcttac	120
tctgctactc ggaaactatt tttatgtaat taatgtatgc tttcttggtt ataaatgcct	180
gatttaaaaa aaaaaaaaaa a	201

&lt;210&gt; 79

&lt;211&gt; 552

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(552)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 79

tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg	60
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt	120
cctctttcct ctgaagatta atgaagtga aaattgaggt ggataaatac aaaaaggtag	180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt	240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact	300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga	360
taataattcta tgttctaataa gttgggctat acataaanta tnaagaaata tggaatttta	420
ttcccaggaa tatgggggttc atttatgaat antaccggg anagaagttt tgantnaaac	480
cngtttttgt taatacgta atagtgcctn aatnaacaag gcntgactta tttccaaaaa	540
aaaaaaaaaa aa	552

&lt;210&gt; 80

&lt;211&gt; 476

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(476)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 80

acagggtatt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga	60
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct	120
cacacagact cccgagtagc tgggactaca ggacacagct cactgaagca ggccctgttt	180
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta	240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt acttccatac	300
tcttctaagt cctcttcag cctcactttg agtcctcctt gggggttgat aggaantntc	360
tcttggtttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat	420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaaa aaaaaa	476

&lt;210&gt; 81

&lt;211&gt; 232

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(232)

&lt;223&gt; n = A,T,C or G

<400> 87  
 agaaaccagt atctctnaaa acaacctctc ataccttggt gacctaatTT tgtgtgcgtg 60  
 tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg 120  
 cctcttttggT atctatatct gtgaaagtTT taatgatctg ccataatgtc ttggggacct 180  
 ttgtcttctg tgtaaagtgt actagagaaa acacctatnt tatgagtcaa tctagtntgt 240  
 tttattcgac atgaaggaaa tttccagatn acaacctna caaactctcc cttgactagg 300  
 ggggacaaag aaaagcnaaa ctgaacatna gaaacaatn cctgggtgaga aattncataa 360  
 acagaaattg ggtngtatat tgaaanannG catcattnaa acgttttttt ttt 413

<210> 88  
 <211> 448  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(448)  
 <223> n = A,T,C or G

<400> 88  
 cgcagcgggt cctctctatc tagctccagc ctctcgctg ccccaactcc cgcgtccgcg 60  
 gtctagccn accatggcgg ggcccctgcg cgcccgcgtg ctctgctgg ccacccctggc 120  
 cgtggccctg gccgtgagcc ccgcgccggg ctccagctcc ggcaagccgc cgcgcctggt 180  
 ggagggccca tggaccccgC gtggaagaag aaggtgtgcg gcgtgcactg gactttgcgc 240  
 tcggcnanta caacaaaccC gcaacnactt ttaccnagcn cgcgtgcag gttgtgccgc 300  
 cccaancaaa ttgttactng gggtaanata ttcttggaag ttgaacctgg gccaaacnng 360  
 tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaagg 420  
 gaancantcc tgntcttttc caaatTTT 448

<210> 89  
 <211> 463  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(463)  
 <223> n = A,T,C or G

<400> 89  
 gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca 60  
 gtagtgattc tgccaaagtT ggtgttgtaa catgagtatg taaaatgtca aaaaattagc 120  
 agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtT 180  
 ctcaagtaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcacT 240  
 tttnatgttn agacttgcct ctntnaaatt gcttttgnT tctgcaggta ctatctgtgg 300  
 ttttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360  
 aattctctcc ccatannaaa acccangccc ttggganaat ttgaaaaang gntccttcnn 420  
 aattcnnana anttcagntn tcatacaaca naacngganc ccc 463

<210> 90  
 <211> 400  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(400)

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca    60
agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattcccag    120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg    180
gcacaccctc ctggggccca ggcgggcacc tgcgtctccc agtatgcaa ctggctgggtg    240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg    300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc    360
agcgttncgg cctcatccgg

```

```

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

```

```

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc    60
tnccatcgtc atactgtagg ttggccacca cctcctgcat cttggggcgg ctaatatcca    120
ggaaactctc aatcaagtca ccgtcnatna aacctgtggc tggttctgtc ttccgctcgg    180
tgtgaaagga tctccagaag gagtgtcga tcttcccac acttttgatg actttattga    240
gtcgattctg catgtccagc aggaggttg accagctctc tgacagtgag gtcaccagcc    300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac    360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggngaa    420
aaagaacacc tcttggaagt gctngccgct cctcgtcent tggtggnngc gentnccttt    481
t

```

```

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt    60
acttgaaaaa gcaacttnaa gcctggacac tgggtattaaa attcacaata tgcaacactt    120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg    180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga    240
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt    300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg    360
atatntgagc ggaagantag cctttctact tcaccagaca caactccttt catattggga    420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg          472

```

```

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

```



&lt;222&gt; (1)...(377)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 93

agaacggctgg	accttgcctc	gcattgtgct	gctggcagga	ataccttggc	aagcagctcc	60
agtcggagca	gccccagacc	gctgccgccc	gaagctaagc	ctgcctctgg	ccttcccctc	120
cgcctcaatg	cagaaccant	agtgggagca	ctgtgttttag	agttaagagt	gaacactgtg	180
tgattttact	tgggaatttc	ctctgttata	tagcttttcc	caatgcta	ttccaaacaa	240
caacaacaaa	ataacatgtt	tgctgttna	gttgataaa	agtangtgat	tctgtatnta	300
aagaaaatat	tactgttaca	tatactgctt	gcaanttctg	tatttattgg	tnctctggaa	360
ataaatatat	tattaa					377

&lt;210&gt; 94

&lt;211&gt; 495

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(495)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 94

ccctttgagg	ggttagggtc	cagttcccag	tggaagaaac	aggccaggag	aantgcgtgc	60
cgagctgang	cagatttccc	acagtgaccc	cagagccctg	ggctatagtc	tctgaccctt	120
ccaaggaaag	accaccttct	ggggacatgg	gctggagggc	aggacctaga	ggcaccaagg	180
gaaggcccca	ttccggggct	gttccccgag	gaggaaggga	aggggctctg	tgtgccqccc	240
acgaggaana	ggccctgant	cctgggatca	nacacccctt	cacgtgtatc	cccacacaaa	300
tgcaagctca	ccaaggtccc	ctctcagtc	cttccctaca	ccctgaacgg	ncactggccc	360
acaccacccc	agancancca	cccgccatgg	ggaatgtnc	caaggaatcg	cngggcaacg	420
tggactctng	ttccnnaagg	gggcagaatc	tccaatagan	gganngaacc	cttgcctnana	480
aaaaaaaaana	aaaaa					495

&lt;210&gt; 95

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(472)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 95

ggttacttgg	tttcattgcc	accacttagt	ggatgtcatt	tagaaccatt	ttgtctgctc	60
cctctggaag	ccttgcgcag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
tagctgtttt	gagttgattc	gcaccactgc	accacaactc	aatatgaaaa	ctatttnact	180
tattttattat	cttgtgaaaa	gtatacaatg	aaaattttgt	tcatactgta	tttatcaagt	240
atgatgaaaa	gcaatagata	tatattcttt	tattatgttn	aattatgatt	gccattatta	300
atcggcaaaa	tgtggagtgt	atgttctttt	cacagtaata	tatgcctttt	gtaacttcac	360
ttggttattt	tattgtaaat	gaattacaaa	attcttaatt	taagaaaatg	gtangttata	420
tttanttcan	taattttctt	ccttgtttac	gttaattttg	aaaagaatgc	at	472

&lt;210&gt; 96

&lt;211&gt; 476

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<223> n = A,T,C or G

<400> 90

agggattgaa ggtctntnt actgtcggac tgttcancca ccaactctac aagttgctgt	60
cttcactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaat	120
tcttcaccag tcacatcttc taggaccttt ttggattcag ttagtataag ctcttccact	180
tcctttgtta agacttcac tggtaaagtc ttaagttttg tagaaaggaa ttttaattgct	240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaaccacc tnaagtcct	300
ttgtgcatcc attttaata tacttaatag ggcattggt cactaggta aattctgcaa	360
gagtcactg tctgcaaaag ttgcgttagt atatctgcc	400

<210> 91

<211> 480

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(480)

<223> n = A,T,C or G

<400> 91

gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact	60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac	120
atgcctcttt gactaccgtg tgccagtgtt ggtgattctc acacacctcc nncgctctt	180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaat tcaccacga	240
gacacttgaa aggtgtaaca aagcgactct tgcatgtctt tttgtccctc cggcaccagt	300
tgtcaatact aaccgctgg tttgcctcca tcacatttgt gatctgtagc tctggataca	360
tctcctgaca gtactgaaga acttctctt ttgtttcaaa agcaactctt ggtgcctgtt	420
ngatcagggt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaa	480

<210> 92

<211> 477

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(477)

<223> n = A,T,C or G

<400> 92

atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggtcact	60
ggtcccgtg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt	120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttg ggttgacggt	180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccagc gtgcgggacc	240
tgcagcgaat ctctcgtatg gtcacgagcg ggaagcgaat gangcccagg gccttgcca	300
gaaccttcg cctgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcgg	360
accagcggac aaacggcggt gaacagccgc acctcacgga tgcccantgt gtcgcgtcc	420
aggaacggcn ccagcgtgct cagggtcaatg tcggtgaanc ctccgcgggt aatggcg	477

<210> 93

<211> 377

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c 171

<210> 100  
 <211> 269  
 <212> DNA  
 <213> Homo sapien

<400> 100

cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcc a gactttggtc 60  
 cgactgcgac gacggcgccg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc 120  
 aaggctgagc tgacgccgca gaggtcgtgt cagctccbac gacottgacg ccgtcgggga 180  
 cagccggaac agagcccggt gaagcgggag gcctcgggga gccctcggg aagggcggcc 240  
 cgagagatac gcaggtgcag gtggccgcc 269

<210> 101  
 <211> 405  
 <212> DNA  
 <213> Homo sapien

<400> 101

tttttttttt ttttggaaac tactgcgagc acagcaggtc agcaacaagt ttattttgca 60  
 gctagcaagg taacagggtta gggcatgggt acatgttcag gtcaacttcc ttgtcgtgg 120  
 ttgattgggt tgtctttatg ggggcggggt ggggtagggg aaacgaagca aataacatgg 180  
 agtgggtgca ccctccctgt agaacctggt tacaagctt ggggcagttc acctgggtctg 240  
 tgaccgtcat tttcttgaca tcaatgttat tagaagtcag gatattcttt agagagtcca 300  
 ctgttctgga gggagattag gggttcttgc caaatccaac aaaatccact gaaaaagtgt 360  
 gatgatcagt acgaataccg aggcataatc tcatatcggg ggcca 405

<210> 102  
 <211> 470  
 <212> DNA  
 <213> Homo sapien

<400> 102

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 ggcaactaat ccatttttat ttcaaaatgt ctacaaattt aatccatta tacgggtattt 120  
 tcaaaatcta aattattcaa attagccaaa tccttaccaa ataataccca aaaatcaaaa 180  
 atatacttct ttcagcaaac ttgttacata aattaaaaaa atatatacgg ctgggtgtttt 240  
 caaagtacaa ttatcttaac actgcaaaaca ttttaaggaa ctaaaataaa aaaaaacact 300  
 ccgcaaagggt taaagggaac aacaaattct tttaacaacac cattataaaa atcatatctc 360  
 aaatcttagg ggaatatata cttcacacgg gatcttaact tttactcact ttgtttattt 420  
 ttttaaacca ttgtttgggc ccaacacaat ggaatccccc ctggactagt 470

<210> 103  
 <211> 581  
 <212> DNA  
 <213> Homo sapien

<400> 103

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 tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac 120  
 taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt 180  
 gaaaatcttc tctagctott ttgactgtaa atttttgact cttgtaaaac atccaaattc 240  
 atttttcttg tctttaaaat tatctaattc ttccattttt tccctattcc aagtcaattt 300  
 gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa 360  
 agggaaaaca ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct 420  
 acgttaataa aatagcattt tgtgaagcca gctcaaaaga aggccttagat ccttttatgt 480  
 ccatttttagt cactaaacga tatcaaagtg ccagaatgca aaaggtttgt gaacatttat 540

<220>  
 <221> misc\_feature  
 <222> (1)...(476)  
 <223> n = A,T,C or G

<400> 96  
 ctgaagcatt tcttcaaact tntctacttt tgtcattgat acctgtagta agttgacaat 60  
 gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt 120  
 ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt 180  
 attcttcaca gtagatgatg aaagagtctt ccagtgtctt gngcanaatg ttctagnat 240  
 agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat 300  
 tgtgttagtc tcaattccta ccacactgag ggaacccctc aaatcactat attcttatct 360  
 gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt 420  
 tacaaagtct atcttctca nangtctgtn aaggaacaat ttaatcttct agcttt 476

<210> 97  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(479)  
 <223> n = A,T,C or G

<400> 97  
 actctttcta atgctgatat gatcttgagt ataagaatgc atatgtcact agaattggata 60  
 aaataatgct gcaaaacttaa tgttcttatg caaaatggaa cgctaataaa acacagctta 120  
 caatcgcaaa tcaaaactca caagtgtcct tctgtttagt atttagtgta ataagactta 180  
 gattgtgctc ctccggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat 240  
 caggctacta gaattctggt attggatatn tgagagcatg aaatttttaa naatacactt 300  
 gtgattatna aattaatcac aaatttctact tatacctgct atcagcagct agaaaaacat 360  
 ntntttttta natcaaagta ttttgtgttt ggaantgttn aaatgaaatc tgaatgtggg 420  
 ttcnatctta tttttcccn gacnactant tnccttttta gggncctattc tganccatc 479

<210> 98  
 <211> 461  
 <212> DNA  
 <213> Homo sapien

<400> 98  
 agtgacttgt cctccaacaa aacccttga tcaagtttgt ggcactgaca atcagaccta 60  
 tgctagtcc tgctatctat tcgctactaa atgcagactg gaggggacca aaaaggggca 120  
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180  
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240  
 tgaagccact ctgaacacgc tggttatcta gatgagaaca gagaaataaa gtcagaaaat 300  
 ttacctggag aaaagaggct ttggctgggg accatcccat tgaaccttct ctttaaggact 360  
 ttaagaaaaa ctaccacatg ttgtgtatcc tgggtccggc cgtttatgaa ctgaccaccc 420  
 tttggaataa tcttgacgct cctgaacttg ctctctcgcg a 461

<210> 99  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 99  
 gtggcgcgc gcaggtgttt cctcgtaaccg cagggccccc tcccttcccc aggcgtccct 60  
 cggcgcctct gcgggcccga ggaggagcgg ctggcgggtg gggggagtgt gacccaccc 120

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ccgctacgac gtgagccgct tgggccgggg caagcgctcg ctagtgctgg acctgaagca 180
gccgcgggga gccgccgtgc tgcggcgctct gtgcaagcgg tcggatgtgc tgctggagcc 240
cttcgccgcg ggtgtcatgg agaaactcca gctgggcca gagattctgc agcgggaaaa 300
tccaagcgtt atttatgcca ggctgagtggt atttggccag tcaggaagct tctgccgggt 360
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tggtgagaat ccgtatgccc cgctgaatct cctggctgac tttgctgggt gtggccttat 480
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a 1621

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<210> 108  
 <211> 382  
 <212> PRT  
 <213> Homo sapien

<400> 108  
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 Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg  
 35 40 45  
 Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala  
 50 55 60  
 Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe  
 65 70 75 80  
 Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln  
 85 90 95  
 Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln  
 100 105 110  
 Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala  
 115 120 125  
 Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr  
 130 135 140  
 Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys  
 145 150 155 160  
 Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys  
 165 170 175  
 Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser  
 180 185 190  
 Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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581

<210> 104  
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<400> 104

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caaaactgct	caaattgttt	gttaagtatt	ccattataat	tagttggcag	gagctaatac	420
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<210> 105  
 <211> 538  
 <212> DNA  
 <213> Homo sapien

<400> 105

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<210> 106  
 <211> 473  
 <212> DNA  
 <213> Homo sapien

<400> 106

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gcaaacgcta	attctcttct	ccatccccat	gtgatattgt	gtatatgtgt	gagttggtag	300
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<210> 107  
 <211> 1621  
 <212> DNA  
 <213> Homo sapien

<400> 107

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<211> 3410  
 <212> DNA  
 <213> Homo sapien

<400> 110

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<210> 109
<211> 1524
<212> DNA
<213> Homo sapien
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<210> 110



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 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Leu Arg Gln  
 180 185 190  
 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu  
 195 200 205  
 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr  
 210 215 220  
 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp  
 225 230 235 240  
 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val  
 245 250 255  
 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg  
 260 265 270  
 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly  
 275 280 285  
 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly  
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 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp  
 305 310 315

<210> 113  
 <211> 553  
 <212> PRT  
 <213> Homo sapien

<400> 113  
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 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
 35 40 45  
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly  
 50 55 60  
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly  
 65 70 75 80  
 Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile  
 85 90 95  
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu  
 100 105 110  
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly  
 115 120 125  
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu  
 130 135 140  
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala  
 145 150 155 160  
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr  
 165 170 175  
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu  
 180 185 190  
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu  
 195 200 205  
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<212> DNA
<213> Homo sapien
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<210> 112
<211> 315
<212> PRT
<213> Homo sapien
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			20					25					30			
Phe	Phe	Leu	Phe	Phe	Leu	Gly	Val	Trp	Leu	Val	Ala	Tyr	Gly	Val	Ala	
		35				40						45				
Thr	Glu	Gly	Leu	Leu	Arg	Pro	Arg	Asp	Ser	Asp	Phe	Pro	Ser	Ile	Leu	
	50					55					60					
Arg	Arg	Val	Phe	Tyr	Arg	Pro	Tyr	Leu	Gln	Ile	Phe	Gly	Gln	Ile	Pro	
65				70						75					80	
Gln	Glu	Asp	Met	Asp	Val	Ala	Leu	Met	Glu	His	Ser	Asn	Cys	Ser	Ser	
			85						90					95		
Glu	Pro	Gly	Phe	Trp	Ala	His	Pro	Pro	Gly	Ala	Gln	Ala	Gly	Thr	Cys	
			100					105					110			
Val	Ser	Gln	Tyr	Ala	Asn	Trp	Leu	Val	Val	Leu	Leu	Leu	Val	Ile	Phe	
		115					120					125				
Leu	Leu	Val	Ala	Asn	Ile	Leu	Leu	Val	Asn	Leu	Leu	Ile	Ala	Met	Phe	
	130					135						140				

Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile  
                             85                            90                            95  
 Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr  
                             100                            105                            110  
 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys  
                             115                            120                            125  
 Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met  
                             130                            135                            140  
 Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp  
                             145                            150                            155                            160  
 Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn  
                             165                            170                            175  
 Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala  
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 His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile  
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 Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly  
                             210                            215                            220  
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<210> 115  
 <211> 366  
 <212> DNA  
 <213> Homo sapien

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 tctcagaacc atttcaccca gacagcctgt ttctatcctg tttaataaat tagtttgggt 300  
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 ttagtc 366

<210> 116  
 <211> 282  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(282)  
 <223> n = A,T,C or G

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 agactttact attttcatat tttaagacac atgatttatc ctatttttagt aacctgggtc 180  
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<210> 117  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

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<210> 114
<211> 241
<212> PRT
<213> Homo sapien
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**<400> 114**

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1				5					10					15	
Leu	Ile	Phe	Leu	Cys	Gly	Ala	Ala	Leu	Leu	Ala	Val	Gly	Ile	Trp	Val
			20					25					30		
Ser	Ile	Asp	Gly	Ala	Ser	Phe	Leu	Lys	Ile	Phe	Gly	Pro	Leu	Ser	Ser
		35				40						45			
Ser	Ala	Met	Gln	Phe	Val	Asn	Val	Gly	Tyr	Phe	Leu	Ile	Ala	Ala	Gly
	50					55					60				
Val	Val	Val	Phe	Ala	Leu	Gly	Phe	Leu	Gly	Cys	Tyr	Gly	Ala	Lys	Thr
65					70					75					80

<210> 121  
 <211> 218  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(218)  
 <223> n = A,T,C or G

<400> 121  
 tgtancgtga anacgacaga naggggtgtc aaaaatggag aanccttgaa gtcattttga 60  
 gaataagatt tgctaaaaga tttggggcta aaacatgggt attgggagac atttctgaag 120  
 atatncangt aaattangga atgaattcat ggttcttttg ggaattcctt tacgatngcc 180  
 agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 122  
 taggggtgta tgcaactgta aggacaaaaa ttgagactca actggcttaa ccaataaagg 60  
 catttgtag ctcatggaac aggaagtggg atgggtggggc atcttcagtg ctgcatgagt 120  
 caccaccccg gcgggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171

<210> 123  
 <211> 76  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(76)  
 <223> n = A,T,C or G

<400> 123  
 tgtagcgtga agacnacaga atggtgtgtg ctgtgctatc caggaacaca tttattatca 60  
 ttatcaanta ttgtgt 76

<210> 124  
 <211> 131  
 <212> DNA  
 <213> Homo sapien

<400> 124  
 acctttcccc aaggccaatg tcctgtgtgc taactggccg gctgcaggac agctgcaatt 60  
 caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120  
 ttaagatttg t 131

<210> 125  
 <211> 432  
 <212> DNA  
 <213> Homo sapien

<400> 125  
 acttttatcta ctggctatga aatagatggg ggaaaattgc gttaccaact ataccactgg 60  
 ctggaaaaag aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa 120

<220>  
 <221> misc\_feature  
 <222> (1)...(305)  
 <223> n = A,T,C or G

<400> 117  
 acacatgtcg cttcactgcc ttcttagatg cttctgggtca acatanagga acagggacca 60  
 tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa 120  
 aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga 180  
 tactgatccc tgatcactgt cctaatagcag gatgtgggaa acagatgagg tcacctctgt 240  
 gactgcccga gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300  
 tgggt 305

<210> 118  
 <211> 71  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(71)  
 <223> n = A,T,C or G

<400> 118  
 accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa 60  
 aantcctggg t 71

<210> 119  
 <211> 212  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(212)  
 <223> n = A,T,C or G

<400> 119  
 actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca 60  
 gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac 120  
 agtaagctgg cccttctaataaaaagaaaat tgaaagggtt ctcactaanc ggaattaant 180  
 aatggantca aganactccc aggcctcagc gt 212

<210> 120  
 <211> 90  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(90)  
 <223> n = A,T,C or G

<400> 120  
 actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggctcttgcc 60  
 ctccgccggc gcagaacatg ctgggggtgg 90

<220>  
 <221> misc\_feature  
 <222> (1)...(362)  
 <223> n = A,T,C or G

<400> 130

ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca	60
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa	120
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa	180
ttctgtattc cattttgtta acgcctggta gatgtaaact gctangaggc taactttata	240
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat	300
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaacttta aaaagtaatg	360
gg	362

<210> 131  
 <211> 332  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 131

ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca	60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga	120
gttctccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc	180
ttctgaacta gattaaggca gcttgtaaag ctgatgtgat ttggtttatt atccaactaa	240
cttccatctg ttatcactgg agaaagccca gactcccan gacnggtacg gattgtgggc	300
atanaaggat tgggtgaagc tggcgttgtg gt	332

<210> 132  
 <211> 322  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(322)  
 <223> n = A,T,C or G

<400> 132

acttttgcca tttgtatat ataaacaatc ttgggacatt ctctgaaaa ctagggtgtcc	60
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat	120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt	180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg	240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct	300
gtaacaatct acaattggtc ca	322

<210> 133  
 <211> 278  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(278)

ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat	180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg	240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt actgcatact tcatggatcc	300
catggtgggg gtcttgcacg tgtaagaatg gaattgattt tgcttttgca agaattctcag	360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaaccctc agtgcctctc	420
ctctttgctt gt	432

<210> 126  
 <211> 112  
 <212> DNA  
 <213> Homo sapien

<400> 126	
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaaccat	60
agtaagaatg atatttcccc ccagggatca ccaaataattt ataaaaattt gt	112

<210> 127  
 <211> 54  
 <212> DNA  
 <213> Homo sapien

<400> 127	
accacgaaac cacaacaag atggaagcat caatccactt gccaaagcaca gcag	54

<210> 128  
 <211> 323  
 <212> DNA  
 <213> Homo sapien

<400> 128	
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc	60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca	120
ttctctctga agtctaggtt acccattttg gggaccatt ataggcaata aacacagtcc	180
ccaaagcatt tggacagttt cttgttggtg tttagaatgg ttttcctttt tcttagcctt	240
ttctgcaaaa aggtcactc agtcccttgc ttgtcagtg gactgggctc cccagggcct	300
aggtgcctt cttttccatg tcc	323

<210> 129  
 <211> 192  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(192)  
 <223> n = A,T,C or G

<400> 129	
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatatc	60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc	120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg	180
gataaacaaa gt	192

<210> 130  
 <211> 362  
 <212> DNA  
 <213> Homo sapien



tcccaggaac cccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg 360  
 ggtgcagang gatgaagcag ccagntgttc tgctgtggt 399

<210> 137  
 <211> 165  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(165)  
 <223> n = A,T,C or G

<400> 137  
 actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt 60  
 ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga 120  
 ttggctggtc ccaactggtg tcaactgtcat tgggtggggt cctgt 165

<210> 138  
 <211> 338  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(338)  
 <223> n = A,T,C or G

<400> 138  
 actcactgga atgccacatt cacaacagaa tcagagggtct gtgaaaacat taatggctcc 60  
 ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa 120  
 tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg 180  
 tcatgtgttt ccagccacac caaaagggtc ttggggtgga gggctggggg catananggt 240  
 cangcctcag gaagcctcaa gtccattca gctttgccac tgtacattcc ccatntttaa 300  
 aaaaactgat gccttttttt ttttttttg taaaattc 338

<210> 139  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 139  
 gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa 60  
 gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccga gtaaggaga 120  
 attcaaacag acctcgtcat tcctggtgtg agcctggtcg gctcaccgcc tatcatctgc 180  
 atttgctta ctcagggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg 240  
 ccttatttgt cttctacacc ccacagggcc ccctaactct tcggatgtgt ttttaataat 300  
 gtcagctatg tgccccatcc tccttcatgc cctccctccc tttctacca ctgctgagtg 360  
 gcctggaact gtgttaaagt gt 382

<210> 140  
 <211> 200  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(200)

<223> n = A,T,C or G

<400> 133

acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt	60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta	120
ctatttaaaa aaaatcacia atctttccct ttaagctatg ttnaattcaa actattcctg	180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt	240
cccacgaaac actaataaaa accacagaga ccagcctg	278

<210> 134

<211> 121

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(121)

<223> n = A,T,C or G

<400> 134

gtttanaaaa cttgttttagc tccatagagg aaagaatggt aaactttgta ttttaaaaca	60
tgattctctg aggttaaact tggttttcaa atgttatatt tacttgtatt ttgcttttgg	120
t	121

<210> 135

<211> 350

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(350)

<223> n = A,T,C or G

<400> 135

acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctataacc	60
atancaagtg gtgactgggt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc	120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtagtcca	180
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct	240
ccacctcaat caagccctgg gccatgtac ctgcaattgg ctgaacaaac gtttgctgag	300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt	350

<210> 136

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(399)

<223> n = A,T,C or G

<400> 136

tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt	60
gctgtgattg tatccgaata ntccctgtga gaaaagataa tgagatgacg tgagcagcct	120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggtctga	180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag	240
aaaactgcag aggccagggt tcaggtgtna gtgggtangt gaccataaaa caccaggtgc	300

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(164)  
 <223> n = A,T,C or G

<400> 144  
 acttcagtaa caacatacaa taacaacatt aagtgtatat,tgccatcttt gtcattttct 60  
 atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaatttg 120  
 aggaatttaa tccatatttg ttttcaataa ggaaaaaag atgt 164

<210> 145  
 <211> 303  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(303)  
 <223> n = A,T,C or G

<400> 145  
 acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa 60  
 actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat 120  
 gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca 180  
 gtaggggagt ccatccaagt gacagggtcta atcaaaggag gaaatggaac ataagcccag 240  
 tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat 300  
 caa 303

<210> 146  
 <211> 327  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(327)  
 <223> n = A,T,C or G

<400> 146  
 actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac 60  
 actggcctgg agtgactcat tgctctggtt ggttgagaga gtccttttc caacaggcct 120  
 ccaagtcagg gctgggattt gtttcccttc cacattctag caacaatatg ctggccactt 180  
 cctgaacagg gaggggtgga ggagccagca tggaacaagc tgccacttcc taaagtagcc 240  
 agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg 300  
 taggggtgag ctgtgtgact ctatggt 327

<210> 147  
 <211> 173  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(173)  
 <223> n = A,T,C or G

<223> n = A,T,C or G

<400> 140

accaaancctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat	60
acttttcatt taacancctt tgtaaagtgt caggctgcac tttgtccat anaattattg	120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatattt	180
atattcagca taaaggagaa	200

<210> 141

<211> 335

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg	60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttggt	120
atgcatgtag agaaccctaa ctaatttatt aaacaggata gaaacaggct gtctgggtga	180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg	240
tttttctacc agttcagaga tnggttaatg actantcca atggggaaaa agcaagatgg	300
attcacaaac caagtaattt taaacaaaga cactt	335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accagggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta	60
gggttggttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat	120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca	180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc	240
ttcaaacatc atagccaatg atgcccgcgt tgcctataat ctctccgaca taaaaccaca	300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga	360
agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct	420
cagcangggg gggaggaacc agctcaacct tggcgtant	459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt ccaccaagtc aggactcctg gcttctgtgg gagttcttat cacctgaggg	60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag	120
accatccgac ttccctgtgt	140

<210> 144

<211> 164

agcaagatgg ctttgaactc aggggtcacca ccagctattg gacottacta tgaaaaccat 120  
 ggataccaac cggaaaaccc ctatcccgca cagccactg tggccccac tgtctacgag 180  
 gtgcatccgg ctca 196

<210> 152  
 <211> 132  
 <212> DNA  
 <213> Homo sapien

<400> 152  
 acagcacttt cacatgtaag aaggagagaaa ttcctaaatg taggagaaag ataacagaa 60  
 cttccccttt tcatctagt gtggaaacct gatgctttat gttgacagga atagaaccag 120  
 gagggagttt gt 132

<210> 153  
 <211> 285  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(285)  
 <223> n = A,T,C or G

<400> 153  
 acaanaccca nganaggcca ctggccgtgg tgcattggcc tccaaacatg aaagtgtcag 60  
 cttctgctct tatgtcctca tctgacaact cttaccatt tttatcctcg ctcagcagga 120  
 gcacatcaat aaagtccaaa gtcttgact tggccttggc ttggaggaag tcatcaacac 180  
 cctggctagt gaggggtgagg cgccgtcctt ggatgacggc atctgtgaag tcgtgcacca 240  
 gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt 285

<210> 154  
 <211> 333  
 <212> DNA  
 <213> Homo sapien

<400> 154  
 accacagtcc tgttgggcca gggttcatg accctttctg tgaaaagcca tattatcacc 60  
 accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac 120  
 cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcttg 180  
 attggcacag gagtcgaagg tttcagctc ccctcctccg tggaacgaga ctctgatttg 240  
 agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg 300  
 gtcaggcctg tctcatccat atggatcttc cgg 333

<210> 155  
 <211> 308  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(308)  
 <223> n = A,T,C or G

<400> 155  
 actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg 60  
 gaaagtgtct tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat 120  
 ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag cccagcccc 180

<400> 147  
 acattgtttt tttagataa agcattgana gagctctcct taacgtgaca caatggaagg 60  
 actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt 120  
 atattcaagc acatatgtta tatattatc agttccatgt ttatagccta gtt 173

<210> 148  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(477)  
 <223> n = A,T,C or G

<400> 148  
 acaaccactt tatctcatcg aatttttaac ccaaactcac tcaactgtgcc ttctatcct 60  
 atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact 120  
 gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg 180  
 gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac 240  
 nccancccac ctcaccgacc ccatcctctt acacagctac ctcccttgctc tctaaccoca 300  
 tagattatnt ccaaattcag tcaattaagt tactattaac actctaccg acatgtccag 360  
 caccactggt aagccttctc cagccaacac acacacacac acacnacac acacacatat 420  
 ccaggcacag gctacctcat cttcacaatc accccttta ttaccatgct atggtgg 477

<210> 149  
 <211> 207  
 <212> DNA  
 <213> Homo sapien

<400> 149  
 acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac 60  
 taacgtatatt tagagagcca aggaagggtt ctgtggggag tgggatgtaa ggtggggcct 120  
 gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca 180  
 tttcaggcag agggaacagc agtgaaa 207

<210> 150  
 <211> 111  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(111)  
 <223> n = A,T,C or G

<400> 150  
 acccttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg 60  
 cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t 111

<210> 151  
 <211> 196  
 <212> DNA  
 <213> Homo sapien

<400> 151  
 agcgcggcag gtcattatga acattccaga tacctatcat tactcgatgc tgttgataac 60

tccaacaaga	actgagggtt	cagagcgggt	agggagaggt	gctgttccag	ttgcacctgg	120
gctgctgtgg	actgttggtt	attcctcact	acggcccaag	gttgtggaac	tggcanaaag	180
gtgtgttggt	gganttgagc	tcgggcgggt	gtggtaggtt	gtgggctctt	caacaggggc	240
tgctgtggtg	ccgggangtg	aangtgttgt	gtcacttgag	cttgccagc	tctggaaaag	300
antanattct	tcctgaaggc	cagcgcttgt	ggagctggca	ngggtcantg	ttgtgtgtaa	360
cgaaccagtg	ctgctgtggg	tgggtgtana	tcctccacaa	agcctgaagt	tatggtgtcn	420
tcaggtaana	atgtgggttc	agtgtccctg	ggcngctgtg	gaaggttgta	nattgtcacc	480
aagggaataa	gctgtggt					498

&lt;210&gt; 160

&lt;211&gt; 380

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(380)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 160

acctgcatcc	agcttccctg	ccaaactcac	aaggagacat	caacctctag	acagggaaac	60
agcttcagga	tacttccagg	agacagagcc	accagcagca	aaacaaatat	tcccatgcct	120
ggagcatggc	atagaggaag	ctganaaatg	tggggtctga	ggaagccatt	tgagtctggc	180
cactagacat	ctcatcagcc	acttgtgtga	agagatgccc	catgacccca	gatgcctctc	240
ccacccttac	ctccatctca	cacacttgag	ctttccactc	tgtataattc	taacatcctg	300
gagaaaaatg	gcagtttgac	cgaacctgtt	cacaacggta	gaggctgatt	tctaacgaaa	360
cttgtagaat	gaagcctgga					380

&lt;210&gt; 161

&lt;211&gt; 114

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 161

actccacatc	ccctctgagc	aggcggttgt	cgttcaaggt	gtatttgccc	ttgcctgtca	60
cactgtccac	tggcccctta	tccacttggt	gcttaatccc	tcgaaagagc	atgt	114

&lt;210&gt; 162

&lt;211&gt; 177

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 162

actttctgaa	tcgaatcaaa	tgatacttag	tgtagtttta	atatcctcat	atatatcaaa	60
gttttactac	tctgataatt	ttgtaaacca	ggtaaccaga	acatccagtc	atacagcttt	120
tggtgatata	taacttggca	ataaccaggt	ctggtgatac	ataaaactac	tcaactgt	177

&lt;210&gt; 163

&lt;211&gt; 137

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(137)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 163

atcacagctc actgctctgt tcattccaggc ccagcatgta gtggctgatt cttcttggt 240  
 gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcattgctg 300  
 gccctggt 308

<210> 156  
 <211> 295  
 <212> DNA  
 <213> Homo sapien

<400> 156  
 accttgctcg gtgcttgga catattagga actcaaaata tgagatgata acagtgccta 60  
 ttattgatta ctgagagaac tgtagacat ttagttgaag attttctaca caggaactga 120  
 gaataggaga ttatgtttgg cctcatatt ctctcctatc ctccttgcc cttctatgt 180  
 ctaatatatt ctcaatcaaa taaggttagc ataacagga aatcgaccaa ataccaatat 240  
 aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat 295

<210> 157  
 <211> 126  
 <212> DNA  
 <213> Homo sapien

<400> 157  
 acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct 60  
 gaagagcaaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc 120  
 cttagt 126

<210> 158  
 <211> 442  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(442)  
 <223> n = A,T,C or G

<400> 158  
 acccaactggt cttggaacaa cccatcctta atacgatgat ttttctgtcg tgtgaaaatg 60  
 aanccagcag gctgccccta gtcagtcctt cctccagag aaaaagagat ttgagaaagt 120  
 gcttggttaa ttcaccatta atttctccc ccaaactctc tgagtcttcc cttaatattt 180  
 ctggtgttgc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta 240  
 natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgggtg 300  
 ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga 360  
 nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg 420  
 tgttcattct ctgatgtcct gt 442

<210> 159  
 <211> 498  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(498)  
 <223> n = A,T,C or G

<400> 159  
 acttccaggt aacgttggtg tttccgttga gcctgaactg atgggtgacg ttgtaggttc 60



<210> 167  
 <211> 247  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(247)  
 <223> n = A,T,C or G

<400> 167  
 acagagccag accttggcca taaatgaanc agagattaag actaaacccc aagtcganat 60  
 tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc 120  
 tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180  
 tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac 240  
 tgangtc 247

<210> 168  
 <211> 273  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(273)  
 <223> n = A,T,C or G

<400> 168  
 acttctaagt tttctagaag tgggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60  
 aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatggt tccacaaagg 120  
 gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag taggggtggc 180  
 aattcccaac ttccttgcca caagcttccc aggctttctc ccttggaana ctccagcttg 240  
 agtcccgatg aactcatggt gctgccctgg gca 273

<210> 169  
 <211> 431  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(431)  
 <223> n = A,T,C or G

<400> 169  
 acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60  
 agctcagacc aggttcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120  
 ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag 180  
 ggacagcaga aggggttant tactgatgga caccatcttc tctgtatact ccacactgac 240  
 cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctg gcaccagctc 300  
 acgcacatca ctgacaaccg ggatggaaaa agaantgcc aatttcatac atccaactgg 360  
 aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420  
 tcgaacactg a 431

<210> 170  
 <211> 266  
 <212> DNA

catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atccccgtgac	60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacett	120
catcagcggc atgatgt	137

<210> 164  
 <211> 469  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(469)  
 <223> n = A,T,C or G

<400> 164	
cttatcacia tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta	60
tgcaatgcat catgctatct catacctaata gagggagttc caggagattc aaccaggaaa	120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt	180
gagacatgca cttgctacga aacagaaatt tcatgttgca ccttggttc tacacctgtg	240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg	300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct	360
tctagtaggc acagggtcc caggccaggc ctcattctcc tctggcctct aatagtcaat	420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt	469

<210> 165  
 <211> 195  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(195)  
 <223> n = A,T,C or G

<400> 165	
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctgggtg	60
atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc	120
tgaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact	180
tcctctgaga tgagt	195

<210> 166  
 <211> 383  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 166	
acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc	60
cgaggtcgga gtccacacca ccggtgtagg tgtgtcaat cttgggcttg gcgcccacct	120
ttggagaagg gatattgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt	180
tttgagacc agcctgagca aggggaggat gttcagcttc agtcctcct tcgtcagggtg	240
gatgccaaac tcgtctangg tccgtgggaa gctgggtgtcc acntcaccta caacctgggc	300
gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt	360
nggggccttt ttggtgaact ttc	383

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro  
 1 5 10 15  
 Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser  
 20 25 30  
 Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr  
 35 40 45  
 Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Ala Asn Gly  
 50 55 60  
 Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu  
 65 70 75 80  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe  
 85 90 95  
 Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser  
 100 105 110  
 Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe  
 115 120 125  
 Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn  
 130 135 140  
 Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
 145 150 155

<210> 173  
 <211> 1265  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(1265)  
 <223> n = A,T,C or G

<400> 173

ggcagcccg	actcgagcc	ctggcagcg	gcactgggtca	tggaacacga	attgttctgc	60
tcgggctgc	tggtgcatcc	gcagtgggtg	ctgtcagccg	cacactgttt	ccagaactcc	120
tacaccatcg	ggctgggcct	gcacagtctt	gagggccgacc	aagagccagg	gagccagatg	180
gtggaggcca	gcctctccgt	acggcaccca	gagtacaaca	gacccttgct	cgctaacgac	240
ctcatgctca	tcaagttgga	cgaatccgtg	tccgagtctg	acaccatccg	gagcatcagc	300
attgcttcgc	agtgccttac	cgcggggaac	tcttgccctg	tttctggctg	gggtctgctg	360
gcgaacgggtg	agctcacggg	tgtgtgtctg	ccctcttcaa	ggaggtcctc	tgcccagtcg	420
cgggggctga	cccagagctc	tgcgtcccag	gcagaatgcc	taccgtgctg	cagtgcgtga	480
acgtgtcggg	ggtgtctgag	gaggtctgca	gtaagctcta	tgaccgctg	taccaccca	540
gcatgttctg	cgccggcgga	gggcaagacc	agaaggactc	ctgcaacggg	gactctgggg	600
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gccaagttgg	cgtgccaggt	gtctacacca	acctctgcaa	attcactgag	tggaatagaga	720
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tcagaccag	gagtcagac	ccccagccc	ctcctccctc	agaccagga	gtccagcccc	960
tcctcctcca	gaccagag	tccagacccc	ctccctcaga	cccaggggtt		1020
gagcccccca	acccctcctc	cttcagagtc	agaggtccaa	gcccccaacc	cctcgttccc	1080
cagaccagga	ggttnaggtc	ccagccctc	ttcctcaga	cccagnggtc	caatgccacc	1140
tagattttcc	ctgnacacag	tgcctccttg	tggngangttg	acccaacctt	accagttggt	1200
ttttcatttt	tngtcccttt	cccctagatc	cagaaataaa	gtttaagaga	ngngcaaaaa	1260
aaaaa						1265

<210> 174  
 <211> 1459  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(266)

<223> n = A,T,C or G

<400> 170

acctgtgggc	tgggctgtta	tgctgtgcc	ggctgtgaa	agggagttca	gaggtggagc	60
tcaaggagct	ctgcaggcat	tttgccaanc	ctctccanag	canagggagc	aacctacact	120
ccccgctaga	aagacaccag	attggagtcc	tgggaggggg	agttgggggtg	ggcatttgat	180
gtatacttgt	cacctgaatg	aangagccag	agaggaanga	gacgaanatg	anattggcct	240
tcaaagctag	gggtctggca	ggtgga				266

<210> 171

<211> 1248

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1248)

<223> n = A,T,C or G

<400> 171

ggcagccaaa	tcataaacgg	cgaggactgc	agcccgcaact	cgagccctg	gcaggcggca	60
ctggtcatgg	aaaacgaatt	gttctgctcg	ggcgctcctgg	tgcatccgca	gtgggtgctg	120
tcagccgcac	actgtttcca	gaagtgagtg	cagagctcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	240
cggcaccacg	agtacaacag	acccttgctc	gctaacgacc	tcagtctcat	caagttggac	300
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gcggggaaact	cttgccctcg	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	420
gtgctgcagt	gcgtgaacgt	gtcggtggtg	tctgaggagg	tctgcagtaa	gctctatgac	480
ccgctgtacc	accccagcat	gttctgcgcc	ggcggagggg	aagaccagaa	ggactcctgc	540
aacggtgact	ctggggggcc	cctgatctgc	aacgggtact	tgaggggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccagggtgtc	acaccaacct	ctgcaaattc	660
actgagtggg	tagagaaaac	cgtccaggcc	agttaactct	ggggactggg	aacctatgaa	720
attgaccccc	aaatacatcc	tgcggaagga	attcaggaat	atctgttccc	agccccctcct	780
ccctcaggcc	caggagtcca	ggccccagc	ccctcctccc	tcaaaccaag	ggtacagatc	840
cccagcccct	cctccctcag	acccaggagt	ccagaccccc	cagccccctc	tccctcagac	900
ccaggagtcc	agccccctcct	ccctcagacc	caggagtcca	gacccccag	cccctcctcc	960
ctcagaccca	gggtccaggg	cccccaacc	ctcctccctc	agactcagag	gtccaagccc	1020
ccaaccctnc	attccccaga	cccagaggtc	cagggtccag	cccctcntcc	ctcagaccca	1080
gcggtccaat	gccacctaga	ctntccctgt	acacagtggc	cccttggtggc	acgttgaccc	1140
aaccttacca	gttggttttt	catttttngt	ccctttcccc	tagatccaga	aataaagttt	1200
aaagagaagng	caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaa		1248

<210> 172

<211> 159

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(159)

<223> Xaa = Any Amino Acid

<400> 172

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gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagaccccc agcccctcnt 840
ccntcagacc caggagtcca gcccctcctc cntcagacgc aggagtccag acccccacgc 900
ccntcntccg tcagaccagc ggggtgcaggc ccccaacccc tcntccntca gagtccagg 960
tccaagcccc caaccctcgc ttccccagac ccagaggtnc aggtcccagc ccctcctccc 1020
tcagaccagc cgggtccaatg ccacctagan tntccctgta cacagtgcgc ccttggtggca 1080
ngttgaccca acctaccag ttgggttttc atttttgtc cctttcccct agatccagaa 1140
ataaagtnta agagaagcgc aaaaaaa 1167

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&lt;210&gt; 176

&lt;211&gt; 205

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(205)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 176

```

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1           5           10           15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
 20           25           30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
 35           40           45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
 50           55           60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
 65           70           75           80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
 85           90           95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
100           105           110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
115           120           125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
130           135           140
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
145           150           155           160
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
165           170           175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
180           185           190
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
195           200           205

```

&lt;210&gt; 177

&lt;211&gt; 1119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 177

```

gcgcactcgc agccctggca ggcggcactg gtcattgaaa acgaattgtt ctgctcgggc 60
gtcctgggtgc atccgcagtg ggtgctgtca gccgcacact gtttcagaa ctctacacc 120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc caggagacca gatgggtggag 180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa ogacctcatg 240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct 300
tcgcagtgcc ctaccgcggg gaactcttgc ctcgtttctg gctgggggtct gctggcgaaac 360

```

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1459)

<223> n = A,T,C or G

<400> 174

ggtcagccgc	acactgtttc	cagaagtgc	tgacagagctc	ctacaccatc	gggctgggccc	60
tgacagctct	tgaggccgac	caagagccag	ggagccagat	ggtaggggccc	agcctctccc	120
tacggcacc	agagtacaac	agacccttgc	tcgctaacga	cctcatgtct	atcaagttgg	180
acgaatccgt	gtccgagctc	gacaccatcc	ggagcatcag	cattgcttcg	cagtgcctta	240
ccgcggggaa	ctcttgccct	gtttctggct	gggtctgtct	ggcgaacggg	gagctcacgg	300
gtgtgtgtct	gccctcttca	aggaggtcct	ctgccagtc	gcgggggctg	accagagct	360
ctgcgtccca	ggcagaatgc	ctaccgtgct	gcagtgcgtg	aacgtgtcgg	tggtgtctga	420
ngaggtctgc	antaagctct	atgaccgct	gtaccacccc	ancatgttct	gcgccggcgg	480
agggcaagac	cagaaggact	cctgcaacgt	gagagagggg	aaaggggagg	gcaggcgact	540
cagggaaagg	tgagaaagg	ggagacagag	acacacaggg	ccgcatggcg	agatgcagag	600
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ataaacacag	gaataaagag	aagcaaagga	agagagaaac	agaaacagac	atggggaggc	720
agaaacacac	acacatagaa	atgcagttga	ccttccaaca	gcattggggc	tgagggcggg	780
gacctccacc	caatagaaaa	tcctcttata	acttttgact	ccccaaaaac	ctgactagaa	840
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gtctgtgaat	ttttttaaat	tgttgcaact	ctcctaaaat	ttttctgatg	tgttttattga	1020
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gtaccagag	ggaaacagtg	acacagattc	atagaggtga	aacacgaaga	gaaacaggaa	1140
aatcaagac	tctacaaaga	ggctgggcag	ggtaggtcat	gcctgtaatc	ccagcacttt	1200
gggaggcgag	gcaggcgagat	cacttgagggt	aaggagttca	agaccagcct	ggccaaaatg	1260
gtgaaatcct	gtctgtacta	aaaatacaaa	agttagctgg	atatggtggc	aggcgctgtg	1320
aatcccagct	acttgggagg	ctgaggcagg	agaattgctt	gaatatggga	ggcagagggt	1380
gaagtgaatt	gagatcacac	cactatactc	cagctggggc	aacagagtaa	gactctgtct	1440
caaaaaaaaa	aaaaaaaaa					1459

<210> 175

<211> 1167

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1167)

<223> n = A,T,C or G

<400> 175

ggcagccct	ggcaggcggc	actggctcatg	gaaaacgaat	tggtctgtct	gggctgctctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc	agaactccta	caccatcggg	120
ctgggctctg	acagtcttga	ggccgaccaa	gagccaggga	gccagatggg	ggaggccagc	180
ctctccgtac	ggcaccacga	gtacaacaga	ctcttgctcg	ctaacgacct	catgctcatc	240
aagttggacg	aatccgtgtc	cgagtctgac	acctccggga	gcatacagcat	tgcttcgcag	300
tgccctaccg	cggggaactc	ttgcctcgtn	tctggctggg	gtctgctggc	gaacggcaga	360
atgcctaccg	tgctgcactg	cgtgaacgtg	tcggtgggtg	ctgaggangt	ctgcagtaag	420
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgcgg	gcggagggca	agaccagaag	480
gactcctgca	acggtgactc	tgggggggccc	ctgatctgca	acgggtactt	gcagggcctt	540
gtgtctttcg	gaaaagcccc	gtgtggccaa	cttggcgtgc	cagggtgtcta	caccaacctc	600
tgcaaatcca	ctgagtggtg	agagaaaacc	gtccagncca	gttaactctg	gggactggga	660
acccatgaaa	ttgaccccc	aatacatcct	gcggaangaa	ttcaggaata	tctgttccca	720
gcccctcctc	cctcaggccc	aggagtccag	gccccagcc	cctcctcct	caaaccaagg	780

aaaaaaaaaa

250

&lt;210&gt; 180

&lt;211&gt; 202

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 180

actagtccag tgtggtggaa ttccattgtg ttggggccaa cacaatggct acctttaaca	60
tcacccagac cccgcccctg cccgtgcccc acgctgctgc taacgacagt atgatgctta	120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttggt tataaatgcc	180
tgatttaaaa aaaaaaaaaa aa	202

&lt;210&gt; 181

&lt;211&gt; 558

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(558)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 181

tccytgtgkt naggtttkkg agacamccck agacctwaan ctgtgtcaca gacttcynng	60
aatgtttagg cagtgttagt aatttcytcg taatgattct gttattactt tcctnattct	120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa	180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca	240
aaattatgca agttagtaat tactcagggg taactaaatt actttaatat gctgttgaaac	300
ctactctgtt ccttggttag aaaaaattat aaacaggact ttgttagttt gggaagccaa	360
attgataata ttctatgttc taaaagttag gctatacata aattattaag aaatatggaw	420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt	480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc	540
caaaaaaaaa aaaaaaaaaa	558

&lt;210&gt; 182

&lt;211&gt; 479

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(479)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 182

acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc	60
agaggggaaa atggggccta gaagttacag mscatytagy tgggtgcgmg gcacccctgg	120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg	180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca	240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca	300
tactmttcta agtcctcttc cagcctcact kkgagtctcm cytggggggt gataggaant	360
ntctcttggc tttctcaata aartctctat ycatctcatg ttttaatttg tacgcatara	420
awtgstgara aaattaaaat gttctgggty mactttaaaa araaaaaaaa aaaaaaaaaa	479

&lt;210&gt; 183

&lt;211&gt; 384

&lt;212&gt; DNA

<213> Homo sapien

<400> 183

aggcgaggagc	agaagctaaa	gccaaagccc	aagaagagt	gcagtgccag	cactgggtgcc	60
agtaccagta	ccaataacag	tgccagtgcc	agtgccagca	ccagtgggtg	cttcagtgtc	120
gggtgccagcc	tgaccgccac	tctcacattt	gggtctctcg	ctggccttgg	tgagctgggt	180
gccagcacca	gtggcagctc	tggtgcctgt	ggtttctcct	acaagtgaga	ttttagatat	240
tgtaaatcct	gccagtcttt	ctcttcaagc	cagggtgcat	cctcagaaac	ctactcaaca	300
cagcactcta	ggcagccact	atcaatcaat	tgaagttgac	actctgcatt	aratctattt	360
gccatttcaa	aaaaaaaaaa	aaaa				384

<210> 184

<211> 496

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(496)

<223> n = A,T,C or G

<400> 184

accgaattgg	gaccgtggc	ttataagcga	tcatgtyynt	ccrgtatcac	ctcaacgagc	60
agggagatcg	agtcctatcg	ctgaagaaat	ttgaccgat	gggacaacag	acctgctcag	120
cccatcctgc	tcggttctcc	ccagatgaca	aatactctsg	acaccgaatc	accatcaaga	180
aacgcttcaa	ggtgctcatg	acccagcaac	cgcgcctgt	cctctgagg	tcccttaaac	240
tgatgtcttt	tctgccacct	gttaccctc	ggagactccg	taaccaaact	cttcggactg	300
tgagccctga	tgctttttg	ccagccatac	tctttggcat	ccagtctctc	gtggcgattg	360
attatgcttg	tgtgaggcaa	tcatggtggc	atcacccata	aagggaacac	atttgacttt	420
tttttctcat	attttaaatt	actacmagaw	tattwmagaw	waaatgawtt	gaaaaactst	480
taaaaaaaaa	aaaaaa					496

<210> 185

<211> 384

<212> DNA

<213> Homo sapien

<400> 185

gctggtagcc	tatggcgkkg	cccacggagg	ggctcctgag	gccacggrac	agtgacttcc	60
caagtatcyt	gcgcsgcgtc	ttctaccgtc	cctacctgca	gatcttcggg	cagattcccc	120
aggaggatcg	ggacgtggcc	ctcatggagc	acagcaactg	yticgtcgag	cccggcttct	180
gggcacaccc	tcctggggcc	caggcgggca	cctgcgtctc	ccagtatgcc	aactggcttg	240
tggtgctgct	cctcgctcatc	ttcctgctcg	tggccaacat	cctgctggtc	aacttgctca	300
ttgccatgtt	cagttacaca	ttcggaag	tacagggcaa	cagcgatctc	tactgggaag	360
gcgcagcggt	accgcctcat	ccgg				384

<210> 186

<211> 577

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(577)

<223> n = A,T,C or G

<400> 186

gagttagctc	ctccacaacc	ttgatgaggt	cgtctgcagt	ggcctctcgc	ttcataccgc	60
------------	------------	------------	------------	------------	------------	----



tnccatcgtc	atactgtagg	tttgccacca	cytcctggca	tcttggggcg	gcntaatatt	120
ccaggaaact	ctcaatcaag	tcaccgtcga	tgaaacctgt	gggctgggtc	tgtcttccgc	180
tcggtgtgaa	aggatctccc	agaaggagtg	ctcgatcttc	cccacacttt	tgatgacttt	240
attgagtcga	ttctgcatgt	ccagcaggag	gttgtaccag	ctctctgaca	gtgaggtcac	300
cagccctatc	atgccgttga	mcgtgccgaa	garcaccgag	ccttgtgtgg	gggkkgaagt	360
ctcaccacga	ttctgcatta	ccagagagcc	gtggcaaaag	acattgacaa	actcgcccag	420
gtggaaaaag	amcamctcct	ggargtgctn	gccgctcctc	gtcmgttggg	ggcagcgctw	480
tccttttgac	acacaaacaa	gttaaaggca	ttttcagccc	ccagaaantt	gtcatcatcc	540
aagatntcgc	acagcactna	tccagttggg	attaaat			577

&lt;210&gt; 187

&lt;211&gt; 534

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(534)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 187

aacatcttcc	tgtataatgc	tgtgtaatat	cgatccgatn	ttgtctgstg	agaatycatw	60
actkggaaaa	gmaacattaa	agcctggaca	ctggtattaa	aattcacaat	atgcaacact	120
ttaaacagtg	tgtcaatctg	ctcccyynac	tttgtcatca	ccagtctggg	aakaagggta	180
tgccctattc	acacctgtta	aaaggcgct	aagcattttt	gattcaacat	cttttttttt	240
gacacaagtc	cgaaaaaagc	aaaagtaaac	agttatyaat	ttgttagcca	attcactttc	300
ttcatgggac	agagccatyt	gatttaaaaa	gcaaattgca	taatattgag	cttyggggagc	360
tgatatttga	gcggaagagt	agcctttcta	cttcaccaga	cacaactccc	tttcatattg	420
ggatgttnac	naaagtwatg	tctctwacag	atgggatgct	tttgtggcaa	ttctgttctg	480
aggatctccc	agttttattta	ccacttgcac	aagaaggcgt	tttcttcctc	agge	534

&lt;210&gt; 188

&lt;211&gt; 761

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(761)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 188

agaaaccagt	atctctnaaa	acaacctctc	ataccttggt	gacctaat	ttgtgtgcgtg	60
ttgtgtgtgcg	cgcatattat	atagacaggc	acatcttttt	tactttttgta	aaagcttatg	120
cctctttgggt	atctatatct	gtgaaagt	taatgatctg	ccataatgtc	ttggggacct	180
ttgtcttctg	tgtaaagtgt	actagagaaa	acacctatnt	tatgagtcaa	tctagttngt	240
tttatttcgac	atgaaggaaa	tttccagatn	acaacactna	caaactctcc	ctkgackarg	300
ggggacaaaag	aaaagcaaaa	ctgamcataa	raaacaatwa	cctggtgaga	arttgcataa	360
acagaaatwr	ggtagtatat	tgaarnacag	catcatataa	rmgttwtktt	wtctccctt	420
gcaaaaaaca	tgtacngact	tcccgttgag	taatgccaa	ttgttttttt	tatnataaaa	480
cttgcccttc	attacatggt	tnaaagtggg	gtgggtggcc	aaaatattga	aatgatggaa	540
ctgactgata	aagctgtaca	aataagcagt	gtgcctaaca	agcaacacag	taatgttgac	600
atgcttaatt	cacaaatgct	aatttcatta	taaatgtttg	ctaaaatata	ctttgaacta	660
ttttctgtgn	ttcccagagc	tgagatntta	gattttatgt	agtatnaagt	gaaaaantac	720
gaaaataata	acattgaaga	aaaananaaa	aaanaaaaaa	a		761

&lt;210&gt; 189

&lt;211&gt; 482

<212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 189  
 tttttttttt tttgccgatn ctactatntt attgcaggan gtgggggtgt atgcaccgca 60  
 caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca 120  
 aagccgcctg ctgcccttctc tgtctgtctc ctgggtgcagg cacatgggga gaccttcccc 180  
 aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag 240  
 tgataggcac aggccaccdg gtacagaccc ctccggctcct gacaggtnga tttcgaccag 300  
 gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc 360  
 aaatttggct ngctcatngaa ngggcanttt tccaanttng gctnngtctt ggtacncttg 420  
 gttcggccca gctccncgtc caaaaantat tcaccnnct ccnaattgct tgcnggnccc 480  
 cc 482

<210> 190  
 <211> 471  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(471)  
 <223> n = A,T,C or G

<400> 190  
 tttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtgggtttg 60  
 aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtntcca 120  
 aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag 180  
 cgcttttgac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt 240  
 taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt 300  
 tgaaaaattt catgtatgca atccaaccaa agaacttnat tggatgatcat gantnctcta 360  
 ctacatcnac cttgatcatt gccaggaacn aaaagttnaa ancacnngt acaaaaaanaa 420  
 tctgtaattn anttcaacct ccgtacngaa aaatnttnt tataactcc c 471

<210> 191  
 <211> 402  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(402)  
 <223> n = A,T,C or G

<400> 191  
 gagggattga aggtctgttc tastgtcggm ctgttcagcc accaactcta acaagttgct 60  
 gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa 120  
 attcttcacc agtcacatct tctaggacct ttttggtatc agttagtata agctcttcca 180  
 cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg 240  
 ctggttctct aacaatgtcc tctccttgaa gtatttggct gaacaacca cctaaagtcc 300  
 ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc 360  
 aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca 402

<210> 192  
 <211> 601  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(601)  
 <223> n = A,T,C or G

<400> 192

gagctcggat	ccaataatct	ttgtctgagg	gcagcacaca	tatncagtgc	catggnaact	60
ggtctacccc	acatgggagc	agcatgccgt	agntatataa	ggtcattccc	tgagtcagac	120
atgcytyttt	gaytaccgtg	tgccaagtgc	tggtgattct	yaacacacyt	ccatcccgt	180
cttttggtga	aaaactggca	cttkctctga	actagcarga	catcacttac	aaattcaccc	240
acgagacact	tgaaagggtg	aacaaagcga	ytcttgcat	gctttttgtc	cctccggcac	300
cagttgtcaa	tactaacccg	ctggtttgcc	tccatcacat	ttgtgatctg	tagctctgga	360
tacatctcct	gacagtactg	aagaacttct	tcttttgttt	caaaagcacc	tcttggtgcc	420
tggtggatca	ggttcccatt	tcccagtcyg	aatgttcaca	tggtcatatt	wacttcccac	480
aaaacattgc	gatttgaggc	tcagcaacag	caaactcctg	tccggcattg	gctgcaagag	540
cctcgatgta	gccgggccagc	gccaaggcag	gcgccgtgag	ccccaccagc	agcagaagca	600
g						601

<210> 193  
 <211> 608  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(608)  
 <223> n = A,T,C or G

<400> 193

atacagccca	natcccacca	cgaagatgcg	cttggtgact	gagaacctga	tgccggtcact	60
ggtcccgtctg	tagccccagc	gactctccac	ctgctggaag	cggttgatgc	tgcaactcytt	120
cccaacgcag	gcagmagcgg	gscgggtcaa	tgaactccay	tcgtggcttg	gggtkgacgg	180
tkaagtgcag	gaagaggctg	accacctcgc	ggtccaccag	gatgcccagc	tgtgcccggac	240
ctgcagcgaa	actcctcgat	ggtcatgagc	gggaagcgaa	tgaggcccag	ggccttgccc	300
agaaccttcc	gcctgttctc	tggtgtcacc	tgcatgtgct	gccgttgaca	ctcgccctcg	360
gaccagcgga	caaacggcrt	tgaacagccg	cacctcacgg	atgccagtg	tgctgcgctc	420
caggammgsc	accagcgtgt	ccaggtcaat	gtcgggtgaag	ccctccgagg	gtrattggcgt	480
ctgcagtggt	tttgtcgatg	ttctccaggc	acaggctggc	cagctgcggg	tcacgaaga	540
gtcgcgcctg	cgtgagcagc	atgaaggcgt	tgctggctcg	cagttcttct	tcaggaactc	600
cacgcaat						608

<210> 194  
 <211> 392  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 194

gaacggctgg	accttgccctc	gcattgtgct	tgctggcagg	gaataccttg	gcaagcagyt	60
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ccagtccgag cagccccaga ccgctgcgc ccgaagctaa gcctgcctct ggccttcccc 120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg 180
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac 240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt 300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg 360
aaataaatat agttattaaa ggtgtcant cc 392

```

```

<210> 195
<211> 502
<212> DNA
<213> Homo sapien

```

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<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

```

```

<400> 195

```

```

ccsttkgagg ggktaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg 60
ccgagctgag gcagatgttc ccacagtgc cccagagacc stgggstata gtytctgacc 120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc 180
aagggaaggc ccatttccgg ggstgttccc cgaggaggaa gggaaagggc tctgtgtgcc 240
cccagagagg aagaggccct ggtcctggg atcagacacc ccttcacgtg tatccccaca 300
caaatgcaag ctcaccaagg tcccctctca gtccccttcc stacaccctg amcggccact 360
gscscacacc caccagagc acgccaccgc ccatggggar tgtgtcaag gartcgcnng 420
gcargctgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt 480
gctnanaaaa aaaaanaaaa aa 502

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```

<210> 196
<211> 665
<212> DNA
<213> Homo sapien

```

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<220>
<221> misc_feature
<222> (1)...(665)
<223> n = A,T,C or G

```

```

<400> 196

```

```

ggttacttgg ttctattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc 60
cctctggaag ccttgcgag agcggacttt gtaattgttg gagaataact gctgaatttt 120
wagctgtttk gagttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga 180
actwatttat tatcttgtga aaagtataac aatgaaaatt ttgttcatac tgtattkac 240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt 300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact 360
tcacttgggt attttattgt aaatgartta caaaattcct aatttaagar aatggtatgt 420
watatttatt tcattaattt ctttcctkgt ttactgwaat ttgaaaaga wtgcagtatt 480
tcttgacaga aatcgatctt gatgctgttg aagtagtttg acccacatcc ctatgagttt 540
ttcttagaat gtataaagg ttagcccat cnaacttcaa agaaaaaat gaccacatac 600
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan 660
aagtg 665

```

```

<210> 197
<211> 492
<212> DNA
<213> Homo sapien

```

```

<220>

```

<221> misc\_feature  
 <222> (1)...(492)  
 <223> n = A,T,C or G

<400> 197

tttntttttt ttttttttgc aggaaggatt ccattttattg tggatgcatt ttcacaatat	60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa nttttttagg	120
aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag	180
aatttatagtc naaccagtaa acnaggaatt tactttttcaa aagattaaat ccaaactgaa	240
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgtac	300
attctcttct gaactttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct	360
tgttcaaaag tacaacnaag caatgttccc ttacatagg ccttaattca aactttgatc	420
catttcactc ccatacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg	480
ancntggctt aa	492

<210> 198  
 <211> 478  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(478)  
 <223> n = A,T,C or G

<400> 198

tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa	60
tgtnctcacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac	120
tgagtatatt ttgaaaagga caagttttaa gtanacncat attgccganc atancacatt	180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat	240
nataatgtc aatcngattt aagatacaaa acagatccta tggtagatan catcntgtag	300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta	360
agcattctag tacctctact ccattggttaa gaatcgtaca cttatgttta catatgnca	420
gggtaagaat tgtgttaagt naanttatgg agagggtccan gagaaaaatt tgatncaa	478

<210> 199  
 <211> 482  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 199

agtgaactgt cctccaacaa aacccttga tcaagtttgt ggcactgaca atcagacct	60
tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca	120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga	180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta	240
tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga	300
aaatttacct ggangaaaag aggttttngg ctggggacca tccattgaa ctttctctta	360
anggacttta agaanaaact accacatgtn tgtngtatcc tgggtgccngg ccgtttantg	420
aacntngacn ncacccttnt ggaatanant cttgacngcn tctgaactt gtcctctgc	480
ga	482

<210> 200  
 <211> 270

<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(270)  
<223> n = A,T,C or G

<400> 200  
cggccgcaag tgcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc 60  
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc 120  
aaggctgagc tgacgccgca gaggtcgtgt caggtccac gaccttgacg ccgtcgggga 180  
cagccggaac agagcccggg gaangcggga ggcctcgggg agcccctcgg gaagggcggc 240  
ccgagagata cgcaggtgca ggtggccgcc 270

<210> 201  
<211> 419  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(419)  
<223> n = A,T,C or G

<400> 201  
tttttttttt ttttggaaac tactgcgagc acagcaggtc agcaacaagt ttattttgca 60  
gctagcaagg taacagggtta gggcatggtt acatgttcag gtcaacttcc ttgtcgtgg 120  
ttgattggtt tgtctttatg ggggcggggg ggggtagggg aaancgaagc anaantaaca 180  
tggagtgggt gcaccctccc tgtagaacct gggtacnaaa gcttggggca gttcacctgg 240  
tctgtgaccg tcattttctt gacatcaatg ttattagaag tcaggatata ttttagagag 300  
tccactgtnt ctggaggagg attagggttt cttgccanaa tccaancaa atccacntga 360  
aaaagtgtga tgatncangt acngaatacc ganggcatan ttctcatant cgggtggcca 419

<210> 202  
<211> 509  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(509)  
<223> n = A,T,C or G

<400> 202  
tttntttttt tttttttttt tttttttttt tttttttttt tttttttttt 60  
tggcacttaa tccattttta tttcaaaatg tctacaaant ttnaatncnc cattatacng 120  
gtntttttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaattnaa 180  
tacnncnaaa aatcaaaaat atacntntct ttcagcaaac ttngttacat aaattaaaaa 240  
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atnttttnaa 300  
ggaactaaaa taaaaaaaaa cactnccgca aagggttaaag ggaacaacaa attcntttta 360  
caacancnnc nattataaaa atcatatctc aaatottagg ggaatatata cttcacacng 420  
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca 480  
caatggnaat nccnccnccncc tggactagt 509

<210> 203  
<211> 583  
<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt ttttttttga cccccctctt ataaaaaaca agttaccatt ttatttttact	60
tacacatatt tatttttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac	120
taaaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt	180
gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc	240
atttttcttg tctttaaaat tatctaactt ttccattttt tccctattcc aagtcaattt	300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa	360
agggaaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc	420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg	480
tccatttttag tcactaaacg atatcnaaag tgccagaatg caaaagggtt gtgaacattt	540
attcaaaagc taatataaga tatttcacat actcatctt ctg	583

<210> 204

<211> 589

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(589)

<223> n = A,T,C or G

<400> 204

ttttttttnt tttttttttt ttttttnctc ttcttttttt ttganaatga ggatcgagtt	60
tttcaactctc tagatagggc atgaagaaaa ctcatctttc cagcttttaa ataacaatca	120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc	180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat	240
tgagagggtt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccctt	300
attttcatgc aaactagaaa ataatgtntt cttttgcata agagaagaga acaatatnag	360
cattacaaaa ctgctcaaat tgtttggtta gnttatccat tataattagt tnggcaggag	420
ctaatacaaa tcacatttac ngacnagcaa taataaaaact gaagtaccag ttaaatatcc	480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat	540
ttattnagaa tgaattcaca tgttattatt ccntagccca acacaatgg	589

<210> 205

<211> 545

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(545)

<223> n = A,T,C or G

<400> 205

ttttnttttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat	60
agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata	120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat	180
ttaagatcat agagcttgta agtgaaaaga taaaatttga cctcagaaac tctgagcatt	240
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat	300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct	360

tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt	420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc ttctatnng	480
aaggattaga tatgtttcct ttgccaatat taaaaaata ataatgttta ctactagtga	540
aacc	545

<210> 206  
 <211> 487  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(487)  
 <223> n = A,T,C or G

<400> 206	
tttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt	60
catttatttag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna	120
caatttataa atgtaagggtg ccattattga gtanatatat tcctccaaga gtggatgtgt	180
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac	240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag	300
ttggttagaa tgcatacanca atctnacaat caacagcaag atgaagctag gcntgggctt	360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cgggtggcaag	420
aactcttcga accgcttcct caaaggcngc tgccacattt gtggcntctn ttgcacttgt	480
ttcaaaa	487

<210> 207  
 <211> 332  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 207	
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa	60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact	120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana	180
atctttgcat gcagaggagg taaaaggat tggattttca cagaggaana acacagcgca	240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg	300
aaaagaaggc agcctaggcc ctggggagcc ca	332

<210> 208  
 <211> 524  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(524)  
 <223> n = A,T,C or G

<400> 208	
agggcgtggt gcgaggggcg ttaactgttt gtctcagtaa caataaatac aaaaagactg	60
gttgtgttcc ggcccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat	120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac	180



tcccgcgtga	ttcacattta	gcaaccaaca	atagctcatg	agtccatact	tgtaaatact	240
tttggcagaa	tacttnttga	aacttgcaga	tgataactaa	gatccaagat	atttcccaaa	300
gtaaatagaa	gtgggtcata	atattaatta	cctgttcaca	tcagcttcca	tttacaagtc	360
atgagccag	acactgacat	caaactaagc	ccacttagac	tcctcaccac	cagtctgtcc	420
tgtcatcaga	caggaggctg	tcaccttgac	caaattctca	ccagtcaatc	atctatccaa	480
aaaccattac	ctgatccact	tccggtaatg	caccaccttg	gtga		524

<210> 209  
 <211> 159  
 <212> DNA  
 <213> Homo sapien

gggtgaggaa	atccagagtt	gccatggaga	aaattccagt	gtcagcattc	ttgctccttg	60
tggccctctc	ctacactctg	gccagagata	ccacagtcaa	acctggagcc	aaaaaggaca	120
caaaggactc	tcgacccaaa	ctgccccaga	ccctctcca			159

<210> 210  
 <211> 256  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(256)  
 <223> n = A,T,C or G

actccctggc	agacaaaggc	agaggagaga	gctctgttag	ttctgtgttg	ttgaactgcc	60
actgaatttc	tttccacttg	gactattaca	tgccanttga	gggactaatg	gaaaaacgta	120
tggggagatt	ttanccaatt	tangtntgta	aatggggaga	ctggggcagg	cgggagagat	180
ttgcaggggtg	naaatgggan	ggctggtttg	ttanatgaac	agggacatag	gaggtaggca	240
ccaggatgct	aatca					256

<210> 211  
 <211> 264  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(264)  
 <223> n = A,T,C or G

acattgtttt	tttgagataa	agcattgaga	gagctctcct	taacgtgaca	caatggaagg	60
actggaacac	ataccacat	ctttgttctg	agggataatt	ttctgataaa	gtcttgctgt	120
atattcaagc	acatatgtta	tatattattc	agttccatgt	ttatagccta	gttaaggaga	180
ggggagatac	attcngaaa	aggactgaaa	gaaatactca	agtnggaaaa	cagaaaaaga	240
aaaaaaggag	caaatgagaa	gcct				264

<210> 212  
 <211> 328  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature

<222> (1)...(328)

<223> n = A,T,C or G

<400> 212

acccaaaaat ccaatgctga atatttggt tcattattcc canattcttt gattgtcaaa	60
ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag	120
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccgccag	180
ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta	240
cccctacnac tctttactct ctgganaggg ccagtgggtg tagctataag cttggccaca	300
tttttttttc ctttattcct ttgtcaga	328

<210> 213

<211> 250

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 213

acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt	60
taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgccca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatata tctctnacct	240
tctcatcggt	250

<210> 214

<211> 444

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(444)

<223> n = A,T,C or G

<400> 214

accagaatc caatgctgaa tatttggtt cattattccc agattctttg attgtcaaag	60
gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg	120
tttatatatg cagcaacaat attcaagcgc gacaacaggc tattgaactt gcccgccagt	180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac	240
ccctacgact ctttactctc tggagagggc cagtgggtgt agctataagc ttggccacat	300
ttttttttcc ttatttcctt tgtcagagat gcgattcatc catatgctan aaaccaacag	360
agtgaacttt acaaaattcc tataganatt gtgaataaaa cottacctat agttgccatt	420
actttgctct ccctaataata cctc	444

<210> 215

<211> 366

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(366)

<223> n = A,T,C or G

&lt;400&gt; 215

acttatgagc	agagcgacat	atccaagtgt	anactgaata	aaactgaatt	ctctccagtt	60
taaagcattg	ctcactgaag	ggatagaagt	gactgccagg	agggaaagta	agccaaggct	120
cattatgcca	aagganatat	acatttcaat	tctccaaact	tcttcctcat	tccaagagtt	180
ttcaatattt	gcatgaacct	gctgataagc	catgttgaga	aacaaatata	tctctgacct	240
tctcatcggt	aagcagaggc	tgtaggcaac	atggaccata	gcgaanaaaa	aacttagtaa	300
tccaagctgt	tttctacact	gtaaccaggt	ttccaaccaa	ggtggaaatc	tcctatactt	360
ggtgcc						366

&lt;210&gt; 216

&lt;211&gt; 260

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(260)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 216

ctgtataaac	agaactccac	tgcangaggg	agggccgggc	caggagaatc	tccgcttgtc	60
caagacaggg	gcctaaggag	ggtctccaca	ctgctnntaa	gggctnttnc	atttttttat	120
taataaaaag	tnnaaaaggc	actttctcaa	cttttttccc	ttnggctgga	aaatttaaaa	180
atcaaaaatt	tcctnaagtt	ntcaagctat	catatatact	ntatcctgaa	aaagcaacat	240
aattcttctt	tcctctcttt					260

&lt;210&gt; 217

&lt;211&gt; 262

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(262)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 217

acctacgtgg	gtaagtttan	aaatgttata	atttcaggaa	naggaacgca	tataattgta	60
tcttgccat	aattttctat	tttaataagg	aaatagcaaa	ttgggggtggg	gggaatgtag	120
ggcattctac	agtttgagca	aaatgcaatt	aaatgtggaa	ggacagcact	gaaaaatttt	180
atgaataatc	tgtatgatta	tatgtctcta	gagtagattt	ataattagcc	acttacccta	240
atatccttca	tgcttgtaaa	gt				262

&lt;210&gt; 218

&lt;211&gt; 205

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(205)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 218

accaaggtgg	tgcattaccg	gaantggatc	aangacacca	tcgtggccaa	cccctgagca	60
cccctatcaa	ctcccttttg	tagtaaaact	ggaaccttgg	aaatgaccag	gccaaagactc	120
aggcctcccc	agttctactg	acctttgtcc	ttangtntna	ngtccagggt	tgctaggaaa	180
anaaatcagc	agacacaggt	gtaaa				205

<210> 219  
 <211> 114  
 <212> DNA  
 <213> Homo sapien

<400> 219  
 tactgttttg tctcagtaac aataaatata aaaagactgg ttgtgttccg gccccatcca 60  
 accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220  
 <211> 93  
 <212> DNA  
 <213> Homo sapien

<400> 220  
 actagccagc acaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60  
 aaataagcat ttagtgctca gtccctactg agt 93

<210> 221  
 <211> 167  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(167)  
 <223> n = A,T,C or G

<400> 221  
 actangtgca ggtgcgcaca aatatttgct gatattccct tcattcttga ttccatgagg 60  
 tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120  
 cccccactac cttccctgac gctcccccana aatcacccaa cctctgt 167

<210> 222  
 <211> 351  
 <212> DNA  
 <213> Homo sapien

<400> 222  
 agggcgtggt gcggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60  
 gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 120  
 atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180  
 ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240  
 taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt 300  
 ctogtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t 351

<210> 223  
 <211> 383  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 223

aaaacaaaca	aacaaaaaaa	acaattcttc	attcagaaaa	attatcttag	ggactgatat	60
tggttaattat	ggtcaattta	atwrrttkt	ggggcatttc	cttacattgt	cttgacaaga	120
ttaaaatgtc	tgtgccaaaa	ttttgtat	tatttgagga	cttcttatca	aaagtaatgc	180
tgccaaagga	agtctaagga	attagtagtg	ttcccmccac	ttggttgagg	tgtgctat	240
taaaagattt	tgatttcctg	gaatgacaat	tatatattta	ctttggtggg	ggaaanagtt	300
ataggaccac	agtcttctact	tctgatactt	gtaaattaat	cttttattgc	acttgttttg	360
accattaagc	tatatgttta	aaa				383

&lt;210&gt; 224

&lt;211&gt; 320

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 224

cccctgaagg	cttcttggtta	gaaaatagta	cagttacaac	caataggaac	aacaaaaaga	60
aaaagtttgt	gacattgttag	tagggagtg	gtacccctta	ctcccatca	aaaaaaaaat	120
ggatacatgg	ttaaaggata	raagggaat	attttatcat	atgttctaaa	agagaaggaa	180
gagaaaatac	tactttctcr	aaatggaagc	ccttaaagg	gctttgatac	tgaaggacac	240
aaatgtggcc	gtccatcctc	ctttaragtt	gcatagactg	gacacggtaa	ctgttgagc	300
tttaractcm	gcattgtgac					320

&lt;210&gt; 225

&lt;211&gt; 1214

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 225

gaggactgca	gcccgcactc	gcagccctgg	caggcggcac	tggtcatgga	aaacgaattg	60
ttctgctcgg	gcgtcctggt	gcataccgag	tggtgctgt	cagccgcaca	ctgtttccag	120
aactcctaca	ccatcgggct	gggcctgcac	agtcttgagg	ccgaccaaga	gccagggagc	180
cagatgggtg	aggccagcct	ctccgtacgg	cacccagagt	acaacagacc	cttgctcgct	240
aacgacctca	tgtcatcaa	gttgagcga	tccgtgtccg	agtctgacac	catccggagc	300
atcagcattg	cttcgcagtg	ccctaccgcg	gggaactctt	gcctcgtttc	tggtgggggt	360
ctgctggcga	acggcagaat	gcctaccgtg	ctgcagtgcg	tgaacgtgtc	ggtggtgtct	420
gaggaggtct	gcagtaagct	ctatgaccgg	ctgtaccacc	ccagcatggt	ctgcgccggc	480
ggagggcaag	accagaagga	ctcctgcaac	ggtgactctg	gggggcccct	gatctgcaac	540
gggtacttgc	agggccttgt	gtctttcgga	aaagccccgt	gtggccaagt	tggtgtgcca	600
ggtgtctaca	ccaacctctg	caaattcact	gagtggatag	agaaaaccgt	ccaggccagt	660
taactctggg	gactgggaac	ccatgaaatt	gacccccaaa	tacatcctgc	ggaagggaatt	720
caggaatatc	tggtcccagc	ccctectccc	tcaggcccag	gagtcagggc	ccccagcccc	780
tcctccctca	aaccaagggt	acagatcccc	agccccctct	ccctcagacc	caggagtcca	840
gacccccag	ccccctctcc	ctcagaccca	ggagtccagc	ccctcctccc	tcagacccag	900
gagtcagac	ccccagccc	ctcctccctc	agacccaggg	gtccaggccc	ccaacccctc	960
ctccctcaga	ctcagaggtc	caagccccca	acccctcctt	ccccagaccc	agaggtccag	1020
gtcccagccc	ctcctccctc	agacccagcg	gtccaatgcc	acctagactc	tcctgttaca	1080
cagtgcctcc	ttgtggcagc	ttgacccaac	cttaccagtt	ggtttttcat	tttttgtccc	1140
tttcccctag	atccagaaat	aaagtctaag	agaagcgcaa	aaaaaaaaaa	aaaaaaaaaa	1200
aaaaaaaaaa	aaaa					1214

&lt;210&gt; 226

&lt;211&gt; 119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 226

accagtatg	tgcagggaga	cggaacccca	tgtgacagcc	cactccacca	gggttcccaa	60
agaacctggc	ccagtcataa	tcattcatcc	tgacagtggc	aataatcacg	ataaccagt	119

<210> 227  
 <211> 818  
 <212> DNA  
 <213> Homo sapien

<400> 227  
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 tttttgctac atatggggtc ccttttcatt ctttgcaaaa acactgggtt ttctgagaac 120  
 acggacgggtt cttagcaciaa tttgtgaaat ctgtgtaraa cggggctttg caggggagat 180  
 aattttctct ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta 240  
 gagaaagcca cgctcggcct tctctgaacc aggatggaac ggcagacccc tgaaaacgaa 300  
 gcttgctccc ttccaatcag ccacttctga gaacccccat ctaacttcct actggaaaag 360  
 agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420  
 ggaaaggggtg caccctcagc agagaagcgg agagcttaac tctggtcgtt tccagagaca 480  
 acctgctggc tgtcttgga tgcccagc ctttgagagg ccactacccc atgaacttct 540  
 gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600  
 gacaggctct gccctcaagc cggctgaggg cagcaaccac tctcctcccc ttctcacgc 660  
 aaagccattc ccacaaatcc agaccatacc atgaagcaac gagaccctaa cagtttggt 720  
 caagaggata tgaggactgt ctgagcctgg ctttggggtg acaccatgca cacacacaag 780  
 gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228  
 <211> 744  
 <212> DNA  
 <213> Homo sapien

<400> 228  
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 gtcatgacgt ttgacatacc tttggaacga gcctcctcct tgggaagatgg aagaccgtgt 120  
 tctgtggcga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180  
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240  
 tgctcgggtg acattggggt gctttgggat aaaagattta tgagccaact attctctggc 300  
 accagattct aggccagttt gttccactga agcttttccc acagcagtc accctctgcag 360  
 gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420  
 gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttg 480  
 ccagacgggtg ttggccactc ccttctaaaa cacaggcgcc ctctgggtga cagtgacccg 540  
 ccgtggtatg ccttggtcca ttccagcagt ccaggttatg catttcaagt ttggggtttg 600  
 ttcttttctg taatgttcct ctgtgtgtgc agctgtcttc atttcctggg ctaagcagca 660  
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720  
 cttcactctg aagtagctgg tgg 744

<210> 229  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 229  
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 tgcagggttg ttgtttttta attattattg ttagaacagt caccacagt ccctgttaat 180  
 ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct 240  
 cactaggctc ctcttgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

## &lt;400&gt; 230

cagcagaaca aatacaata tgaagagtgc aaagatctca taaaatctat gctgaggaat 60  
 gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg 120  
 caatataaag tcctggttca cactcaggaa cgagagctga ccaggttaag ggagaagttg 180  
 cggaaggga gagatgcctc cctctcattg aatgagcatc tccaggecct cctcactccg 240  
 gatgaaccgg acaagtccca ggggcaggac ctccaagaaa cagacctcgg ccgcgaccac 300  
 g 301

## &lt;210&gt; 231

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

## &lt;400&gt; 231

gcaagcacgc tggcaaatct ctgtcaggtc agctccagag aagccattag tcatttttagc 60  
 caggaaactcc aagtccacat ccttggaac tggggacttg cgcagggttag ccttgaggat 120  
 ggcaacacgg gacttctcat caggaagtgg gatgtagatg agctgatcaa gacggccagg 180  
 tctgaggatg gcaggatcaa tgatgtcagg ccggttggtta ccgccaatga tgaacacatt 240  
 tttttttgtg gacatgccat ccatttctgt caggatctgg ttgatgactc ggtcagcagc 300  
 c 301

## &lt;210&gt; 232

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

## &lt;400&gt; 232

agtaggtatt tcgtgagaag ttcaacacca aaactggaac atagttctcc ttcaagtgtt 60  
 ggcgacagcg gggcttcctg attctggaat ataactttgt gtaaatatac agccacctat 120  
 agaagagtcc atctgctgtg aaggagagac agagaactct gggttccgtc gtcctgtcca 180  
 cgtgctgtac caagtgcctg tgccagcctg ttacctgttc tcaactgaaa tctggctaatt 240  
 gctcttgtgt atcacttctg attctgacaa tcaatcaatc aatggcctag agcactgact 300  
 g 301

## &lt;210&gt; 233

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

## &lt;400&gt; 233

atgactgact tccagtaag gctctctaag gggtaagtag gaggatccac aggatttgag 60  
 atgctaaggc ccagagatc gtttgatcca accctcttat ttccagaggg gaaaatgggg 120  
 cctagaagtt acagagcatc tagctggtgc gctggcacc cttggcctcac acagactccc 180  
 gagtagctgg gactacaggc acacagtcac tgaagcaggc cctgttagca attctatgag 240  
 taaaaattaa catgagatga gtagagactt tattgagaaa gcaagagaaa atcctatcaa 300  
 c 301

## &lt;210&gt; 234

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

## &lt;400&gt; 234

aggtcctaca catcgagact catccatgat tgatatgaat ttaaaaatta caagcaaaga 60  
 cattttattc atcatgatgc tttcttttgc ttctttcttc cgttttcttc tttttctttt 120  
 tcaatttcag caacatactt ctcaatttct tcaggattta aaatcttgag ggattgatct 180  
 cgctcatga cagcaagttc aatgtttttg ccacctgact gaaccacttc caggagtgc 240  
 ttgatcacca gcttaatggg cagatcatct gcttcaatgg cttcgtcagt atagttcttc 300

t

301

<210> 235  
 <211> 283  
 <212> DNA  
 <213> Homo sapien

<400> 235

tggggctgtg	catcaggcgg	gtttgagaaa	tattcaattc	tcagcagaag	ccagaatttg	60
aattccctca	tcttttaggg	aatcatttac	caggtttgga	gaggattcag	acagctcagg	120
tgctttcaact	aatgtctctg	aacttctgtc	cctctttggt	catggatagt	ccaataaata	180
atgttatctt	tgaactgatg	ctcataggag	agaatataag	aactctgagt	gatatcaaca	240
ttagggattc	aaagaaatat	tagatttaag	ctcacactgg	tca		283

<210> 236  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 236

aggtcctcca	ccaactgcct	gaagcacggg	taaaattggg	aagaagtata	gtgcagcata	60
aatactttta	aatcgatcag	atttccctaa	cccacatgca	atcttcttca	ccagaagagg	120
tcggagcagc	atcattaata	ccaagcagaa	tgctgaatag	ataaatacaa	tggtatatag	180
tgggtagacg	gcttcattag	tacagtgtac	tgtggtatcg	taatctggac	ttgggttgta	240
aagcatcgtg	taccagtcag	aaagcatcaa	tactcgacat	gaacgaatat	aaagaacacc	300
a						301

<210> 237  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 237

cagtggtagt	ggtggtggac	gtggcggttg	tcgtggtgcc	ttttttggtg	cccgtcacaa	60
actcaatttt	tgctcgctcc	tttttggcct	tttccaattt	gtccatctca	attttctggg	120
ccttggctaa	tgctcatag	taggagtcct	cagaccagcc	atggggatca	aacatatcct	180
ttgggtagtt	ggtgccaagc	tcgtcaatgg	cacagaatgg	atcagcttct	cgtaaactca	240
gggttcgcaa	attctttctt	cctttggata	atgtagttca	tatccattcc	ctcctttatc	300
t						301

<210> 238  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 238

gggcagggtt	tttttttttt	ttttttgatg	gtgcagaccc	ttgctttatt	tgtctgactt	60
gttcacagtt	cagccccctg	ctcagaaaaa	caacgggcca	gctaaggaga	ggaggaggca	120
ccttgagact	tccggagtgc	aggctctcca	gggttcccca	gcccataaat	cattttctgc	180
acccctgccc	tgggaagcag	ctccctgggg	gggtgggaatg	ggtgactaga	agggatttca	240
gtgtggggacc	cagggtctgt	tcttcacagt	aggaggtgga	agggatgact	aattttctta	300
t						301

<210> 239  
 <211> 239  
 <212> DNA  
 <213> Homo sapien



&lt;400&gt; 239

ataagcagct	aggggaattct	ttatttagta	atgtcctaac	ataaaagttc	acataactgc	60
ttctgtcaaa	ccatgatact	gagctttgtg	acaaccaga	aataactaag	agaaggcaaa	120
cataatacct	tagagatcaa	gaaacattta	cacagttcaa	ctgtttaaaa	atagctcaac	180
attcagccag	tgagtagagt	gtgaatgcc	gcatacacag	tatacaggtc	cttcagga	239

&lt;210&gt; 240

&lt;211&gt; 300

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 240

ggtcctaag	aagcagcagc	ttccacattt	taacgcaggt	ttacgggat	actgtccttt	60
gggatctgcc	ctccagtgga	accttttaag	gaagaagtg	gcccagcta	agttccacat	120
gctgggtgag	ccagatgact	tctgttccct	ggtcactttc	ttcaatgggg	cgaatggggg	180
ctgccaggtt	tttaaaatca	tgcttcatct	tgaagcacac	ggtcacttca	ccctcctcac	240
gctgtgggtg	tactttgatg	aaaataccca	ctttgttggc	ctttctgaag	ctataatgtc	300

&lt;210&gt; 241

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 241

gaggtctggt	gctgaggtct	ctgggctagg	aagaggagtt	ctgtggagct	ggaagccaga	60
cctcttttga	ggaaactcca	gcagctatgt	tgggtgtctt	gagggaatgc	aacaaggctg	120
ctcctccatg	tattggaaaa	ctgcaaactg	gactcaactg	gaaggagtg	ctgctgccag	180
tgtgaagaac	cagcctgagg	tgacagaaac	ggaagcaaac	aggaacagcc	agtcttttct	240
tcctcctcct	gtcatacggg	ctctctcaag	catcctttgt	tgtcaggggc	ctaaaaggga	300
g						301

&lt;210&gt; 242

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 242

ccgaggtcct	gggatgcaac	caatcactct	gtttcacgtg	acttttatca	ccatacaatt	60
tgtggcattt	cctcattttc	tacattgtag	aatcaagagt	gtaaaataat	gtatatcgat	120
gtcttcaaga	atatatcatt	cctttttcac	tagaaccat	tcaaaatata	agtcaagaat	180
cttaatatca	acaaatatat	caagcaaact	ggaaggcaga	ataactacca	taatttagta	240
taagtaccca	aagttttata	aatcaaaagc	cctaatagata	accattttta	gaattcaatc	300
a						301

&lt;210&gt; 243

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 243

aggtaagtc	cagtttgaag	ctcaaaagat	ctggtatgag	cataggctca	tcgacgacat	60
ggtggcccaa	gctatgaaat	cagagggagg	cttcatctgg	gcctgtaaaa	actatgatgg	120
tgacgtgcag	tcggactctg	tggcccaagg	gtatggctct	ctcggcatga	tgaccagcgt	180
gctggtttgt	ccagatggca	agacagtaga	agcagaggct	gcccacggga	ctgtaacccg	240
tcactaccgc	atgttccaga	aaggacagga	gacgtccacc	aatcccattg	cttccatttt	300
t						301

&lt;210&gt; 244

<211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 244  
 gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa 60  
 gtcattgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120  
 ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaaagac acatcctaaa 180  
 aggtgttgta atgggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca 240  
 actgtttgtc ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc 300

<210> 245  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 245  
 gtctgagtat ttaaaatggt attgaaatta tccccaacca atggttagaaa agaaagaggt 60  
 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120  
 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180  
 gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatac 240  
 agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa 300  
 g 301

<210> 246  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 246  
 ggtctgtcct acaatgcctg cttcttgaaa gaagtcggca ctttctagaa tagctaaata 60  
 acctgggctt attttaaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120  
 agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180  
 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240  
 caaatgtgtc ttacaaaaca cgttcctaac aaggatgtct ttacactacc aatgcagaaa 300  
 c 301

<210> 247  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 247  
 aggtcctttg gcagggtcga tggatcagag ctcaaactgg agggaaaggc atttcgggta 60  
 gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttgttt cccccacgct 120  
 gtgtcctgtg ttcagggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180  
 ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg gggtccttgc 240  
 cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300  
 a 301

<210> 248  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 248  
 aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60  
 attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt 120

acaggaagaa agtggtttg aagacagcca aagaaataaa agcagattaa attgtatcag 180  
 gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag 240  
 ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300  
 c 301

<210> 249  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 249  
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 ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcatctc cgccccgcc 120  
 ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc 180  
 catcgtaatg aattattttg aaaattaatt ccaecatcct ttcagattct ggatggaaag 240  
 actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt 300  
 a 301

<210> 250  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 250  
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 cttatcttta ttggcttgat aaacataatt atttctaaca ctactttatt tccagttgcc 120  
 cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac 180  
 ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240  
 caataaaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300  
 a 301

<210> 251  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 251  
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 agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat 120  
 ggcagggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct 180  
 cattggggtc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccgga 240  
 cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct 300  
 c 301

<210> 252  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 252  
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 ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120  
 tcattccttt ttactagga acccattcaa aatataagtc aagaatctta atatcaacaa 180  
 atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag taccctaaagt 240  
 tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300  
 a 301

<210> 253

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 253

ttccctaaga agatgttatt ttgttgggtt ttgttcccc tccatctcga ttctcgtagc	60
caactaaaaa aaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctcccttagct	120
tggtctgatt gttttcagac cttaaaatat aaacttggtt cacaagcttt aatccatgtg	180
gatttttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt	240
tccatagtgc ccacagggtg ttccctcacat tttctccata ggaaaatgct ttttccaag	300
g	301

<210> 254  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 254

cgctgcgcct ttcccttggg ggagggggcaa ggccagaggg ggtccaagtg cagcacgagg	60
aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaaatcccc	120
ccaaatctct tcatcttacc ctggtggact cctgactgta gaattttttg gttgaaacaa	180
gaaaaaaata aagcttttga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc	240
acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc	300
t	301

<210> 255  
 <211> 302  
 <212> DNA  
 <213> Homo sapien

<400> 255

agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtc tttattataa	60
attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagt tgacttggat	120
tgggattttg ttgagttcct caagcatctc ctaataccct caagggcctg agtagggggg	180
aggaaaaagg actggagggtg gaatctttat aaaaaacaag agtgattgag gcagattgta	240
aacattatta aaaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac	300
aa	302

<210> 256  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 256

gttccagaaa acattgaagg tggcttccca aagtctaact agggatacce cctctagcct	60
aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc	120
acccccaaaa gcctggacac cttgagcaca cagttatgac caggacagac tcatctctat	180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt	240
gtggcctctc ggctgggtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt	300
t	301

<210> 257  
 <211> 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 257

gttggtggagg aactctggct tgctcattaa gtcctactga ttttactat cccctgaatt	60
tccccactta ttttgtctt tcaactatcg aggccctaga agaggtctac ctgcctccag	120
tottacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat	180
gtcacattac tcccttcagt gattttctgt agaagtgcc atccctgaat gccaccaaga	240
tcttaatctt cacatcttta atcttatctc tttgactcct ctttacaccg gagaaggctc	300
c	301

&lt;210&gt; 258

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(301)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 258

cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc	60
aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc	120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg	180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat	240
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac	300
t	301

&lt;210&gt; 259

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(301)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 259

tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg	60
gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccagtgggaa	120
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt	180
tccagctcac atctcatctg catgcagcac ggaccggatg cgccactgg gtcttggctt	240
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccaggtgg	300
c	301

&lt;210&gt; 260

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 260

tttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaa at aagcaatggt	60
aaggtgtctt aacttgaaaa agattaggag tcaactggtt acaagttata attgaatgaa	120
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac	180
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc	240
actgagacat cagtacctgc ccggcgggcc gctcgagccg aattctgcag atatccatca	300

c

301

<210> 261  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 261  
 aaatattcga gcaaattcctg taactaatgt gtctccataa aaggctttga actcagtga 60  
 tctgcttcca tccacgattc tagcaatgac ctctcggaca tcaaagctcc tcttaagggt 120  
 agcaccaact attccataca attcatcagc aggaaataaa ggctcttcag aagggtcaat 180  
 ggtgacatcc aattttcttct gataatttag attcctcaca accttcctag ttaagtgaag 240  
 ggcgatgatga tcatccaaag cccagtggtc acttactoca gactttctgc aatgaagatc 300  
 a 301

<210> 262  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 262  
 gaggagagcc tggtacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc 60  
 tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaattc ctgagtcacc 120  
 cctagacttc ctaaaaccaga tcctctgggg ctggaacctg gcaactctgca tttgtaatga 180  
 gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtccc 240  
 catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat 300  
 c 301

<210> 263  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 263  
 tttagcttgt ggtaaatgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg 60  
 aaaattacta cttaatccta attcacaata acaatggcat taagggttga cttgagttgg 120  
 ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat 180  
 taatgactga cttcccagta aggtctctta aggggtaagt angaggatcc acaggatttg 240  
 agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg 300  
 g 301

<210> 264  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 264  
 aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc 60  
 aatgaatgac tctaaaaaca atatttacat ttaatgggtt gtagacaata aaaaaacaag 120  
 gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag 180  
 ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac 240  
 acccttcata taaattcact atcttggtt gaggcactcc ataaaatgta tcacgtgcat 300  
 a 301

<210> 265  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 265  
 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcattctttgt 60  
 cttcttgtga cgcagtattt cttctctggg gagaagccgg gaagtcttct cctggctcta 120  
 catattcttg gaagtctcta atcaactttt gttccatttg tttcatttct tcaggaggga 180  
 ttttcagttt gtcaacatgt tctctaacaa cacttgccca tttctgtaa gaatccaaag 240  
 cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300  
 c 301

<210> 266  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 266  
 tacctgtctgc ccttcctccc atccaggcca tctgcgaatc tacatgggtc ctctatttcg 60  
 acaccagatc actctttcct ctaccacag gcttgctatg agcaagagac acaacctcct 120  
 ctcttctgtg ttccagcttc ttttctgtt cttcccaccc ctttaagtct attcctgggg 180  
 atagagacac caatacccat aacctctctc ctaagcctcc ttataacca ggggtgcacag 240  
 cacagactcc tgacaactgg taaggccaat gaactgggag ctacagctg gctgtgctg 300  
 a 301

<210> 267  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 267  
 aaagagcaca ggccagctca gcctgcctg gccatctaga ctacgcctgg ctccatgggg 60  
 gttctcagtg ctgagtccat ccaggaaaag ctacacctaga ctttctgagg ctgaatcttc 120  
 atcctcacag gcagcttctg agagcctgat attcctagcc ttgatgggtc ggagtaaagc 180  
 ctcatctga ttcctctcct tcttttctt caagttggct ttctcacat cctctgttc 240  
 aattcgcttc agcttgtctg ctttagccct catttcaga agcttcttct ctttggcatc 300  
 t 301

<210> 268  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 268  
 aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt tttcttctta 60  
 gatcttggga gagctggtc ttctaaggag aaggaggaag gacagatgta actttggatc 120  
 tcgaagagga agtctaattg aagtaattag tcaacggctc ttgtttagac tcttggaata 180  
 tgcctgggtg ctcagtgagc ccttttgag aaagcaagta ttattcttaa ggagtaacca 240  
 cttccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact 300  
 a 301

<210> 269  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

&lt;400&gt; 269

taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat	60
aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact	120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta	180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta	240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc	300
t	301

&lt;210&gt; 270

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 270

cattgaagag cttttgcgaa acatcagaac acaagtgtt ataaaattaa ttaagcctta	60
cacaagaata catattcctt ttatttctaa ggagttaaac atagatgtag ctgatgtgga	120
gagcttgctg gtgcagtgc tattggataa cactattcat ggccgaattg atcaagtcaa	180
ccaactcctt gaactggatc atcagaagaa ggggtgtgca cgatatactg cactagataa	240
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaaa	300
a	301

&lt;210&gt; 271

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(301)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 271

aaaaggttct cataagatta acaatttaaa taaatatttg atagaacatt ctttctcatt	60
tttatagctc atcttttagg ttgatattca gttcatgtt cccttgctgt tcttgatcca	120
gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggccaagg	180
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt	240
tctctcctcc agatganaac tgatcatgag cccacattt gggttttata gaagcagtca	300
c	301

&lt;210&gt; 272

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 272

taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaagtgc	60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga	120
tccaataatt ccctcatgat gagcaagaaa aattctttgc gcaccctcc tgcatccaca	180
gcattcttct caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgtttct	240
ctaaggactt ccattgcate tcctacaata ttttctctac gcaccactag aattaagcag	300
g	301

&lt;210&gt; 273

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;



<221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 273  
 acatgtgtgt atgtgtatct ttgggaaaaan aanaagacat cttgtttayt atttttttgg 60  
 agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa 120  
 gaaccgtcta aaaataaaat ttaccatgtc dtatatctct tatagtatgc ttatttcacc 180  
 ttytttctgt ccagagagag tatcagtgac ananatttma gggagaamac atgmattggg 240  
 gggacttnty tttaacngagm accctgcccg sgccgcccctg makcngantt ccgcsananc 300  
 t 301

<210> 274  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 274  
 cttatatact ctttctcaga ggcaaaagag gagatgggta atgtagacaa ttcttttgagg 60  
 aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa 120  
 tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttggt gaaaagtcca 180  
 tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc 240  
 aattgtgctt cttttgataa gaagctttct tggcatatc aggaaattcc aganaaagtc 300  
 c 301

<210> 275  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 275  
 tcggtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg 60  
 gggtgaaatt ggccaacttt ctattaactt atgttggtgaa ttttgccacc aacagtaagc 120  
 tggcccttct aataaaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag 180  
 tcaagagact cccaggcctc agcgtacctg cccgggaggc cgctcgaagc cgaattctgc 240  
 agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttgcgccat 300  
 a 301

<210> 276  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 276  
 tgtacacata ctcaataaat aaatgactgc attgtgggtat tattactata ctgattatat 60  
 ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat 120  
 taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc 180  
 caatacatth aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt 240

aaaactattc agtatgtttc ctttgcttca tgtctgagaa ggctctcctt caatggggat 300  
g 301

<210> 277  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 277  
tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60  
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120  
gaatcatggc actcctgata ctttcccaaa tcaacactct caatgccccca ccctcgtcct 180  
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga 240  
gttcnctgtc gattacatct gaccagtctc ctttttccga agtcnctccg ttcaatcttg 300  
c 301

<210> 278  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 278  
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60  
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgca 120  
cagtctctac tggtattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180  
aatgaacatc tcatgtgtgc tcacaatgtt ctggcactat tataagtgtc tcacaggttt 240  
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt 300  
c 301

<210> 279  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 279  
aaagcaggaa tgacaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact 60  
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120  
ttagaccttt accttccagc caccacacag tgcttgatat ttcagagtca gtcattgggt 180  
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240  
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag 300  
a 301

<210> 280

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 280  
 ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60  
 tagaaagggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120  
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg 180  
 gtttgatata gtttaggggtt ggggttagat taagatctaa attacatcag gacaaagaga 240  
 cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300  
 t 301

<210> 281  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 281  
 aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatatctc 60  
 gccgagcaat ccaaactcctg aatgaagggg catcttctga aaaaggagat ctgaatctca 120  
 atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180  
 tgtgtagcac actgcgatta cagctaaata acccgatttt gtgtgtcatg tttgcatttc 240  
 tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagt gcagtacctc 300  
 g 301

<210> 282  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 282  
 caggtaactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60  
 tccagaaccc aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga 120  
 agcgagaag caaagcccag gcagaacat gctaacctta cagctcagcc tgcacagaag 180  
 cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240  
 cagaagcaaa gcccgaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300  
 a 301

<210> 283  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 283  
 atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60  
 cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120  
 gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc 180  
 acttcccagg ttttatgcaa aaattttggt aaattctata atggtgatat gcatctttta 240  
 ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt 300  
 g 301

<210> 284  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 284  
 caggtaacaaa acgctattaa gtggccttaga atttgaacat ttgtggtctt tattttacttt 60

gcttcgtgtg	tgggcaaagc	aacatcttcc	ctaaatatat	attaccaaga	aaagcaagaa	120
gcagattagg	tttttgacaa	aacaaacagg	ccaaaagggg	gctgacctgg	agcagagcat	180
ggtgagaggc	aaggcatgag	agggcaagtt	tggtgtggac	agatctgtgc	ctactttatt	240
actggagtaa	aagaaaacaa	agttcattga	tgtcgaagga	tatatacagt	gtagaaatt	300
a						301

```
<210> 285
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G
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<400> 285						
acatcaccat	gatcggatcc	cccaccatt	atacgttgta	tgtttacata	aatactcttc	60
aatgatcatt	agtgttttaa	aaaaaatact	gaaaactcct	tctgcatccc	aatctctaac	120
caggaaagca	aatgctat	acagacctgc	aagccctccc	tcaaacnaaa	ctatttctgg	180
attaaatatg	tctgacttct	tttgaggtca	cacgactagg	caaatgctat	ttacgatctg	240
caaaagctgt	ttgaagagtc	aaagcccca	tgtgaacacg	atttctggac	cctgtaacag	300
+						301

<210> 286  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 286						
taccactgca	ttccagcctg	ggtgacagag	tgagactccg	tctccaaaaa	aaactttgct	60
tgtatattat	ttttgcctta	cagtggatca	ttctagtagg	aaaggacagt	aagatttttt	120
atcaaaatgt	gtcatgccag	taagagatgt	tatattcttt	tctcatttct	tccccacca	180
aaaataagct	accatatagc	ttataagtct	caaatttttg	ccttttacta	aaatgtgatt	240
gtttctgttc	attgtgtatg	cttcatcacc	tatattaggc	aaattccatt	ttttcccttg	300
t						301

```
<210> 287
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 287						
tacagatctg	ggaactaaat	attaaaaatg	agtgtggctg	gatatatgga	gaatgttggg	60
cccagaagga	acgtagagat	cagatattac	aacagctttg	ttttgagggt	tagaaatatg	120
aaatgatttg	gttatgaacg	cacagtttag	gcagcagggc	cagaatcctg	accctctgcc	180
ccgtggttat	ctcctcccca	gcttggtctg	ctcatgttat	cacagtattc	cattttgttt	240
gttgcatgtc	ttgtgaagcc	atcaagattt	tctcgtctgt	tttcctctca	ttggtaatgc	300
t						301

```
<210> 288
<211> 301
<212> DNA
<213> Homo sapien
```

<400> 288  
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag 60  
agtcaatagg aagacaaatt ccagttccag ctcagttctgg gtatctgcaa agctgcaaaa 120

```

gatcttttaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatac 180
aaaagcatct gcttttgtga ttttaatttag ctcatctggc cactggaaga atccaaacag 240
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa 300
a                                     301

```

```

<210> 289
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 289
ggtacactgt ttccatgtta tgtttctaca cattgctacc tcagtgtcc tggaaactta 60
gcttttcatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg 120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa 180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggccggcgaan aagagaaaga 240
tgtgttttgt tttggactct ctgtggtccc ttccaatgct gtgggtttcc aaccagnnga 300
a                                     301

```

```

<210> 290
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac 60
tgactgatct gttcatttct ctccagctc ttaccccaa aagcttttcc accctaagtg 120
ttctgacctc cttttctaata cacagtaggg atagaggcag anccacctac aatgaacatg 180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctgacagtgc 240
tgccttgaac aaaaacattt ctccatgtct catthttctc atgcctcaag taacagtggag 300
a                                     301

```

```

<210> 291
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 291
caggtaacaa tttcttctat cctagaacaa tttcatttta tgttgttgaa acataacaac 60
tatatcagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc 120
tttactcttt tgtttatagg tgaatcacia aatgtatttt tatgtattct gtagttcaat 180
agccatggct gtttaactta ttttaattat ttagcataaa gacattatga aaaggcctaa 240
acatgagctt cacttcccca ctaactaatt agcatctggt atttcttaac cgtaatgcct 300
a                                     301

```

```

<210> 292
<211> 301
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 292  
 accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc 60  
 tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc 120  
 aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg 180  
 ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240  
 tcactacaca cacagacccc acagtccctat atgccacaaa cacatttcca taacttgaaa 300  
 a 301

<210> 293  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 293  
 ggtaccaagt gctgggtgcc gctgtttacc tgtttctcact gaaaagtctg gctaattgctc 60  
 ttgtgtagtc atttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt 120  
 aacacaaaacg tcaactagcaa agtagcaaca gctttaagtc taaatacaaa gctgtttctgt 180  
 gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg 240  
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcggcc gctcgagcat 300  
 g 301

<210> 294  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 294  
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 attcaataaa attaccttta ttcacacatc tcaaaacaat tctgcaaatt cttagtgaag 120  
 tttaactata gtcacaganc ttaaataatc acattgtttt ctatgtctac tgaaaataag 180  
 ttactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc 240  
 cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt 300  
 t 301

<210> 295  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 295  
 gtactctttc tctcccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta 60  
 cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120  
 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccactctctga 180  
 actggtagaa aaacrtctga agagctagtc tatcagcatc tgacagggtga attggatggt 240  
 tctcagaacc atttcaccca gacagcctgt ttctatcctg ttaataaat tagtttgggt 300  
 tctct 305

<210> 296  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 296

aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct	60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg	120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac	180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt	240
tgctcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg	300
c	301

<210> 297  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(300)

<223> n = A,T,C or G

<400> 297

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aagggttttg aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga	120
acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt	180
tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtgggc	240
accgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactggcgg	300

<210> 298  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 298

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ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg	120
tgaagctctc agatcaatca cgggaagggc ctggcggttg tgccacctg gaaccaccct	180
gtcctgtctg ttacatttc actaycagg tttctctggg cattacnatt tgttccccta	240
caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcagggtggc ctgagcgagg	300
t	301

<210> 299  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 299

gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggctctctgc	60
tcactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct ccaggttagc	120
tgggattgca ggtcacgcc accataccca gctaattttt ttgtattttt agtagagacg	180
gagtttcgcc atgttggcc gctggtctca aactcctgac ctcaagcgac ctgctgcctc	240

cggcctccca aagtgetgga attataggca tgagtcaaca cgcccagcct aaagatatatt 300  
t 301

<210> 300  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 300  
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gctgcattcc acaaggttct cagcctaatt agtttacta cctgccagtc tcaaaactta 180  
gtaaagcaag accatgacat tccccacgg aaatcagagt ttgccccacc gtcttggtac 240  
tataaagcct gcctctaaca gtccttgctt cttcacacca atcccagagc catcccccat 300  
g 301

<210> 301  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 301  
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agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120  
gggaactcac aaagaccctc agagctgaga caccacacac agtgggagct cacaagacc 180  
ctcagagctg agacaccac aacagtggga gtcacaaaag accctcagag ctgagacacc 240  
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300  
t 301

<210> 302  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 302  
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tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac 120  
ttgagttggt tcttagtatt atttatggta aataggctct taccacttgc aaataactgg 180  
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240  
caggatttga gatgctaagg cccagagat cgtttgatcc aaccctctta ttttcagagg 300  
g 301

<210> 303  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 303  
aggtaccaac tgtggaaata ggtagaggat cattttttct ttccatatca actaagttgt 60  
atattgtttt ttgacagttt aacacatctt cttctgtcag agattctttc acaatagcac 120  
tggtaatgg aactaccgct tgcattgtaa aatgggtggt ttgtgaaatg atcataggcc 180  
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240  
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300  
c 301

<210> 304  
<211> 301  
<212> DNA



<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 319  
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 catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120  
 taagattggg tttatgtgat tttagtgggt a 151

<210> 320  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 320  
 aactagtgga tccactagtc cagtgtgggtg gaattccatt gtgttggggt tctagatcgc 60  
 gaggcggtgc cctttttttt tttttttttg ggggggaatt tttttttttt aatagttatt 120  
 gagtgttcta cagcttacag taaataccat 150

<210> 321  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 321  
 agcaactttg tttttcatcc aggttatattt aggcttagga tttcctctca cactgcagtt 60  
 taggggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120  
 tgcctctgag aaatcaaagt cttcatacac t 151

<210> 322  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 322  
 atccagcatc ttctcctggt tcttgccctc ctttttcttc ttcttasatt ctgcttgagg 60  
 tttgggcttg gtcagtttgc cacagggtt ggagatgggt acagtcttct ggcattcggc 120  
 attgtgcagg gctcgttca nacttccagt t 151

<210> 323  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 323  
 tgaggacttg tktttttttt ctttatattt aatcctctta ckttgtaa atattgccta 60  
 nagactcant tactaccag tttgtgggtt twtgggagaa atgtaactgg acagttagct 120  
 gttcaatyaa aaagacactt anccccatgt g 151

105

1		5		10		15									
Pro	His	Ser	Gln	Pro	Trp	Gln	Ala	Ala	Leu	Val	Met	Glu	Asn	Glu	Leu
		20					25						30		
Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp	Val	Leu	Ser	Ala	Thr
		35					40					45			
His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu
	50				55					60					
Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met	Val	Glu	Ala			
65					70					75					

&lt;210&gt; 330

&lt;211&gt; 70

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 330

cccaacacaa tggcccgatc ccatacctga ctccgccctc aggatcgctc gtctctggta  
gctgcagcca

60

70

&lt;210&gt; 331

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 331

Gln	His	Asn	Gly	Pro	Ile	Pro	Ser	Leu	Thr	Pro	Pro	Ser	Gly	Ser	Leu
1			5				10					15			
Val	Ser	Gly	Ser	Cys	Ser										
			20												

&lt;210&gt; 332

&lt;211&gt; 2507

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 332

tggtgccgct	gcagccggca	gagatggttg	agctcatggt	cccgtgttg	ctcctccttc	60
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gtacatcaac	tggtcagctt	cctgggaaag	tagttgtggt	cacaggagct	aatacaggta	180
tcgggaagga	gacagccaaa	gagctggctc	agagaggagc	tcgagtatat	ttagcttgcc	240
gggatgtgga	aaagggggaa	ttggtggcca	aagagatcca	gaccacgaca	gggaaccagc	300
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gcttcottagc	tgaggaaaag	cacctccacg	ttttgatcaa	caatgcagga	gtgatgatgt	420
gtccgtactc	gaagacagca	gatggctttg	agatgcacat	aggagtcaac	cacttgggtc	480
acttcctcct	aacccatctg	ctgctagaga	aactaaagga	atcagcccca	tcaaggatag	540
taaattgtgtc	ttccctcgca	catcacctgg	gaaggatcca	cttcataaac	ctgcagggcg	600
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cagaaggctct	tgagattcta	agtgggaatc	atttcagtga	ctgtcatgtg	gcatgggtct	900
ctgcccgaagc	tcgtaatgag	actatagcaa	ggcggctgtg	ggacgtcagt	tgtgacctgc	960
tgggcctccc	aatagactaa	caggcagtgc	cagttggacc	caagagaaga	ctgcagcaga	1020
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ctagagatat	cataatagga	taagaagacc	ctcatatgac	ctgcacagct	oattttcctt	1260
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gggtcccagcc cctcctccct cagaccagc ggtccaatgc cacctagact ctccctgtac 1080
acagtgeccc cttgtggcac gttgacccaa ccttaccagt tggtttttca tttttgtcc 1140
ctttcccta gatccagaaa taaagtctaa gagaagcgca aaaaaaaaaa aaaaaaaaaa 1200
aaaaaaaaa aaaaa 1215

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<210> 327
<211> 220
<212> PRT
<213> Homo sapien

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<400> 327
Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met
1      5      10      15
Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val
20     25     30
Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
35     40     45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
50     55     60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
65     70     75     80
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
85     90     95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
100    105    110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
115    120    125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
130    135    140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
145    150    155    160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
165    170    175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
180    185    190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
195    200    205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
210    215    220

```

```

<210> 328
<211> 234
<212> DNA
<213> Homo sapien

```

```

<400> 328
cgctcgtctc tggtagctgc agccaatca taaacggcga ggactgcagc ccgactcgc 60
agccctggca ggcggcactg gtcattgaaa acgaattggt ctgctcgggc gtcctgggtgc 120
atccgcagtg ggtgctgtca gccacacact gtttccagaa ctctacacc atcgggctgg 180
gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag gccca 234

```

```

<210> 329
<211> 77
<212> PRT
<213> Homo sapien

```

```

<400> 329
Leu Val Ser Gly Ser Cys Ser Gln Ile Ile Asn Gly Glu Asp Cys Ser

```

gagtggcaga	gtggtgccaa	ccctgttttc	ccagtccacg	tagacagatt	cacagtgcgg	1920
aattctggaa	gctggagaca	gacgggctct	ttgcagagcc	gggactctga	gagggacatg	1980
agggcctctg	cctctgtgtt	cattctctga	tgtcctgtac	ctgggctcag	tgcccgggtg	2040
gactcatctc	ctggccgcgc	agcaaagcca	gcgggttcgt	gctggtcctt	cctgcacctt	2100
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gccagctctc	ctagaaaccc	cgcggcgccg	gccgcagcca	agtgtttatg	gcccgcggtc	2340
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aacaaaaaaa	aaaaaaaaaa	aaaactcgag				3030

&lt;210&gt; 334

&lt;211&gt; 2417

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 334

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gaatgctgac	cattgaggat	atctaaactt	agatcaattg	cattttccct	ccaagactat	300
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tatgccagat	atatgtaaaa	gcaacctaca	agctctctaa	tcagctcac	ctaaaagatt	420
cccgggatct	aataggctca	aagaaacttc	ttctagaaat	ataaaagaga	aaattggatt	480
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cagaatgcat	cctcctacta	atgaggctcag	tacacatttg	cattttaaaa	tgccctgtcc	660
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gcttcagccc	aggagttcaa	gaccagcctg	ggcaacatag	aaagacccca	tctctcaatc	780
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agggagtatt	ttcacaaagt	tcaaaacagc	cacaataatc	agagatggag	caaaccagtg	1620
ccatccagtc	tttatgcaaa	tgaaatgctg	caaagggag	cagattctgt	atatgttggt	1680
aactaccac	caagagcaca	tggttagcag	ggaagaagta	aaaaaagaga	aggagaatac	1740
tggaagataa	tgcacaaaat	gaagggacta	gttaaggatt	aactagccct	ttaaggatta	1800
actagttaag	gattaatagc	aaaagayatt	aaatatgcta	acatagctat	ggaggaattg	1860
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&lt;211&gt; 3030

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 333

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 <213> Homo sapien

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 Pro Lys Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln  
 35 40 45  
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 Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln  
 65 70 75 80  
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 100 105 110  
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&lt;210&gt; 335

&lt;211&gt; 2984

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 335

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<213> Homo sapien

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<212> DNA  
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<210> 344  
<211> 536  
<212> DNA  
<213> Homo sapien

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&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 339

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 Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu  
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 Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val  
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 100 105 110  
 Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala  
 115 120 125  
 Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met  
 130 135 140  
 His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu  
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 Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser  
 165 170 175  
 Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly  
 180 185 190  
 Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala  
 195 200 205  
 Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly  
 210 215 220  
 Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val  
 225 230 235 240  
 Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe  
 245 250 255  
 Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu  
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 Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His  
 275 280 285  
 Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg  
 290 295 300  
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 305 310 315

&lt;210&gt; 340

&lt;211&gt; 483

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 340

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 <213> Homo sapien

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 <212> DNA  
 <213> Homo sapien

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 <211> 251  
 <212> DNA  
 <213> Homo sapien

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&lt;210&gt; 345

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 345

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&lt;210&gt; 346

&lt;211&gt; 282

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(282)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 346

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aggagacta tacctggctc ttgccctaag tgagaggctt tccctcccgc accaaaaaat 180
agaaaggctt tctatttcac tggcccagggt agggggaagg agagtaactt tgagtctgtg 240
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&lt;210&gt; 347

&lt;211&gt; 201

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(201)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 347

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taaataatac ttttaaaana ntactancag cttttaccta ngctcctaaa tgcttgtaaa 120
tctgagactg actggaccca ccagaccca gggcaaagat acatgttacc atatcatctt 180
tataaagaat ttttttttgt c 201

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&lt;210&gt; 348

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 348

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ctgttaatca caacatttgt gcatcacttg tgccaagtga gaaaatgttc taaaatcaca 60
agagagaaca gtgccagaat gaaactgacc ctaagtccca ggtgcccttg ggcaggcaga 120

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tcatctgcaa aataggtcta ggattttcttc caaccatttc atgagttgtg aagctaaggc	480
tttgtaatac atggaaaaag gtagacttat gcagaaagcc tttctggctt tcttatctgt	540
ggtgtctcat ttgagtgtg tccagtgaca tgatcaagtc aatgagtaaa attttaaggg	600
attagatttt cttgacttgt atgtatctgt gagatcttga ataagtgacc tgacatctct	660
gcttaaagaa aaccag	676

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 <211> 574  
 <212> DNA  
 <213> Homo sapien

<400> 356	
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caagcttccc attttagat ctgagtcct atgagtatct gacacctgtt cctctcttca	180
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aaaagtccac aaaactgcag tctttgctgg gatagtaagc caagcagtgc ctggacagca	300
gagttctttt cttgggcaac agataaccag acaggactct aatcgtgctc ttattcaaca	360
ttcttctgtc tctgcctaga ctggaataaa aagccaatct ctctcgtggc acaggggaagg	420
agatacaagc tctgttacat gtgatagatc taacaaaggc atctaccgaa gtctggtctg	480
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agctttgcag cctttgtgca acagtacttt ccca	574

<210> 357  
 <211> 393  
 <212> DNA  
 <213> Homo sapien

<400> 357	
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taatatggkg kcttggtcac tatacttaaa aatgcaccac tcataaatat ttaattcagc	120
aagccacaac caaracttga ttttatcaac aaaaaccctt aaatataaac ggsaaaaaag	180
atagatataa ttattccagt ttttttaaaa cttaaaarat attccattgc cgaattaara	240
araarataag tggttatgg aaagaagggc attcaagcac actaaaraaa cctgaggkaa	300
gcataatctg tacaaaatta aactgtcctt tttggcattt taacaaattt gcaacgktct	360
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<210> 358  
 <211> 630  
 <212> DNA  
 <213> Homo sapien

<400> 358	
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gcatagagta gggaagctaa tccagcacag ggaggtcaca gagacatccc taagggaagt	180
gagtttaaac tgagagaagc aagtgtctaa actgaaggat gtgttgaaga agaagggaga	240
gtagaacaat ttgggcagag ggaaccttat agaccctaag gtgggaaggt tcaaagaact	300
gaaagagagc tagaacagct ggagccgttc tccggtgtaa agaggagtca aagagataag	360
attaaagatg tgaagattaa gatcttggtg gcattcaggg attggcactt ctacaagaaa	420
tcaactgaagg gagtaatgtg acattacttt tcaacttcagg atggccattc taactccagg	480
gggtagactg gactaggtaa gactggaggc aggtagacct cttctaaggc ctgcatagat	540
gaaagacaaa aataagtggg gaaattcagg ggatagttaa aatcagtagg acttaatgag	600
caagccagag gttcctccac aacaaccagt	630

<210> 359  
 <211> 620  
 <212> DNA

&lt;400&gt; 352

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caggctgcgt tccgtcctta cgatgaagac cacgatgcag tttccaaaca ttgccactac	180
atacatggaa aggaggggga agccaacca gaaatgggct ttctctaate ctgggatacc	240
aataagcaca a	251

&lt;210&gt; 353

&lt;211&gt; 436

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 353

tttttttttt tttttttttt ttttttacia caatgcagtc atttttttat tgagtatgtg	60
cacattatgg tattattact atactgatta tattttatcat gtgacttcta attaraaaat	120
gtatccaaaa gcaaaacagc agatatacaa aattaaagag acagaagata gacattaaca	180
gataaggcaa cttatacatt gacaatccaa atccaatata tttaaacatt tgggaaatga	240
gggggacaaa tggaagccar atcaaatttg tgtaaaacta ttcagtatgt ttcccttgct	300
tcatgtctga raaggctctc ccttcaatgg ggatgacaaa ctccaaatgc cacacaaatg	360
ttaacagaat actagattca cactggaacg ggggtaaaga agaaattatt ttctataaaa	420
gggtccttaa tgtagt	436

&lt;210&gt; 354

&lt;211&gt; 854

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 354

ccttttctag ttcaccagtt ttctgcaagg atgctgggta gggagtgtct gcaggaggag	60
caagtctgaa accaaatcta ggaaacatag gaaacgagcc aggcacaggg ctggtggggc	120
atcaggggacc accctttggg ttgatatttt gcttaatctg catcttttga gtaagatcat	180
ctggcagtag aagctgttct ccaggtagat ttctctagct catgtacaaa aacatcctga	240
aggactttgt cagggtgcctt gctaaaagcc agatgcgttc ggcacttctt tggctctgagg	300
ttaattgcac acctacaggg actgggctca tgctttcaag tattttgtcc tcactttagg	360
gtgagtgaag gatccccatt ataggagcac ttgggagaga tcatataaaa gctgactctt	420
gagtacatgc agtaatgggg tagatgtgtg tgggtgtgtc tcattctctg aagggtgctt	480
gtagggaggt gtttccagga ggaacaagtc tgaaaccaat catgaaataa atggtaggtg	540
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caatatggaa ggctctaatt tgcccatatt tgaaataata attcagcttt ttgtaataca	660
aaataacaaa ggattgagaa tcatggtgtc taatgtataa aagaccaggg aaacataaat	720
atatcaactg cataaatgta aaatgcatgt gacccaagaa ggccccaag tggcagacaa	780
cattgtaccc attttccctt ccaaaatgtg agcggcgggc ctgctgcttt caaggctgtc	840
acacgggatg tcag	854

&lt;210&gt; 355

&lt;211&gt; 676

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 355

gaaattaagt atgagctaaa ttccctgtta aaacctctag ggggtacaga tctcttcaac	60
cagggtcaaaag ctgatctttc tggaatgtca ccaaccaagg gcctatattt atcaaaagcc	120
atccacaagt catacctgga tgtcagcgaa gagggcacgg aggcagcagc agccactggg	180
gacagcatcg ctgtaaaaag cctaccaatg agagctcagt tcaaggcgaa ccaccccttc	240
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ccctaatacag atgggggttga gtaaggctca gagttgcaga tgaggtgcag agacaatcct	360
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<210> 363  
 <211> 653  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(653)  
 <223> n = A,T,C or G

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 tgggaggcac tacgcaagat gggactgcgt cctgggggtga gacatcctct ccttgagat 180  
 ctaacgaaac ttctcaccta tgagttgtaa agcagaaata cctgnactac agacgagtgc 240  
 ccaacagcaa ccccccgaa gtatgagttc ctctrgggcc tccgttccta ccatgagasc 300  
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 attttgaga tccntgggtcc agaattccat ttaccttctg ggccagatac caccagaatg 600  
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<210> 364  
 <211> 401  
 <212> DNA  
 <213> Homo sapien

<400> 364  
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 aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180  
 tgagaaagct caattataga tgcaaaagtt taaactaaact actatagtag taaagaaata 240  
 catttcacac ccttcatata aattcactat cttggcttga ggcaactccat aaaatgtatc 300  
 acgtgcatag taaatcttta tatttgctat ggcgttgac tagaggactt ggactgcaac 360  
 aagtggatgc gcggaaaatg aaatcttctt caatagccca g 401

<210> 365  
 <211> 356  
 <212> DNA  
 <213> Homo sapien

<400> 365  
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 taccagagca tcaagtctct gcagcaggtc attcttgggt aaagaaatga cttccacaaa 180  
 ctctccatcc cctggctttg gcttcggcct tgcgttttcg gcatcatctc cgtaaatggt 240  
 gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300  
 acattcggca atgtccctt tgtagccagt ttcttcttcg agctcccga gagcag 356

<210> 366  
 <211> 1851  
 <212> DNA  
 <213> Homo sapien

<400> 366  
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&lt;213&gt; Homo sapien

&lt;400&gt; 359

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ctcaccagaa	gaataaagtg	ctctgccagt	tattaaagga	ttactgctgg	tgaattaaat	180
atggcattcc	ccaagggaaa	tagagagatt	cttctggatt	atgttcaata	tttatttcac	240
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aacaaaaagc	tcacaccaa	caaaaccatc	aacttatttt	gtattctata	acatacgaga	600
ctgtaaagat	gtgacagtgt					620

&lt;210&gt; 360

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 360

aaaaaaaaa	agccagaaca	acatgtgata	gataatatga	ttggctgcac	acttcagac	60
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&lt;210&gt; 361

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 361

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&lt;210&gt; 362

&lt;211&gt; 463

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 362

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taacattgac	gtgtgtaagg	gccagtcttc	cgtatttggg	agctcaagca	taacttgaat	1140
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&lt;210&gt; 369

&lt;211&gt; 1853

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 369

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aagatacatc	aacattttgc	tcaagtagag	ggctgactat	acttgctgat	ccacaacata	360
cagcaagtat	gagagcagtt	cttccatata	tatccagcgc	atttaaattc	gcttttttct	420
tgattaaaaa	tttcaccact	tgctgttttt	gctcatgtat	accaagtagc	agtgggtgta	480
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&lt;210&gt; 367

&lt;211&gt; 668

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 367

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aaaaaaaa						668

&lt;210&gt; 368

&lt;211&gt; 1512

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 368

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## &lt;210&gt; 372

## &lt;211&gt; 1059

## &lt;212&gt; DNA

## &lt;213&gt; Homo sapien

## &lt;400&gt; 372

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 <211> 2184  
 <212> DNA  
 <213> Homo sapien

<400> 370

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<210> 371  
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 <212> DNA  
 <213> Homo sapien

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aaaaaaaaaa	aaaaaaaaaa					2000

&lt;210&gt; 375

&lt;211&gt; 2040

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 375

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&lt;210&gt; 376

&lt;211&gt; 329

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 376

Met Asp Ile Val Val Ser Gly Ser His Pro Leu Trp Val Asp Ser Phe

<210> 373  
 <211> 1155  
 <212> DNA  
 <213> Homo sapien

<400> 373

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<210> 374  
 <211> 2000  
 <212> DNA  
 <213> Homo sapien

<400> 374

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gacaagctcc	acagagctgc	ctggtggggt	aaagtcccca	gaaaggatct	catcgatcatg	480
ctcaggga	ctgacgtgaa	caagaaggac	aagcaaaaaga	ggactgctct	acatctggcc	540
tctgccaatg	ggaattcaga	agtagtaaaa	ctcctgctgg	acagacgatg	tcaacttaat	600
gtccttgaca	acaaaaagag	gacagctctg	ataaaggccg	tacaatgcca	ggaagatgaa	660
tgtgcgttaa	tgttgctgga	acatggcact	gatccaaata	ttccagatga	gtatggaaat	720
accactctgc	actacgctat	ctataatgaa	gataaattaa	tggccaaaagc	actgctctta	780
tatggtgctg	atatcgaatc	aaaaaacaag	catggcctca	caccactgtt	acttggtgta	840
catgagcaaa	aacagcaagt	cgtgaaat	ttaatcaaga	aaaaagcgaa	tttaaatgca	900
ctggatagat	atggaaggac	tgctctcata	cttgctgtat	gttggtggatc	agcaagtata	960
gtcagccttc	tacttgagca	aaatattgat	gtatcttctc	aagatctatc	tggaacagacg	1020
gccagagagt	atgctgtttc	tagtcatcat	catgtaattt	gccagttact	ttctgactac	1080
aaagaaaaac	agatgctaaa	aatctcttct	gaaaacagca	atccagaaca	agacttaaaag	1140
ctgacatcag	aggaagagtc	acaaaaggtc	aaaggcagtg	aaaatagcca	gccagagaaa	1200
atgtctcaag	aaccagaaat	aaataaggat	gggtatagag	aggttgaaag	agaaatgaaag	1260
aagcatgaaa	gtaataatgt	gggattacta	gaaaacctga	ctaattggtgt	cactgctggc	1320
aatggtgata	atggattaat	tcctcaaagg	aagagcagaa	cacctgaaaa	tcagcaattt	1380
cctgacaacg	aaagtgaaga	gtatcacaga	atttgcgaa	tagtttctga	ctacaaagaa	1440
aaacagatgc	caaaatactc	ttctgaaaac	agcaaccag	aacaagactt	aaagctgaca	1500

125

35 40 45  
 Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu  
 50 55 60  
 Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp  
 65 70 75 80  
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp  
 85 90 95  
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro  
 100 105 110  
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp  
 115 120 125  
 Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser  
 130 135 140  
 Lys Asn Lys Val  
 145

<210> 378  
 <211> 1719  
 <212> PRT  
 <213> Homo sapien

<400> 378  
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys  
 1 5 10 15  
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe  
 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285

124

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      1           5           10           15
Leu His Leu Ala Gly Ser Asp Leu Leu Ser Arg Ser Leu Met Ala Glu
      20           25           30
Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
      35           40           45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
      50           55           60
Pro Gln Arg Leu Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
      65           70           75           80
Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val
      85           90           95
Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr
      100          105          110
His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp
      115          120          125
Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp
      130          135          140
Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser
      145          150          155          160
Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys
      165          170          175
Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
      180          185          190
Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly
      195          200          205
Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
      210          215          220
Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr
      225          230          235          240
Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu
      245          250          255
Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
      260          265          270
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
      275          280          285
Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
      290          295          300
Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu
      305          310          315          320
Ser Met Leu Phe Leu Val Ile Ile Met
      325

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&lt;210&gt; 377

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(148)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 377

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Met Thr Xaa Pro Ser Trp Ser Pro Gly Thr Thr Ser Val Glu Lys Ile
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Trp Thr Ser Ser Thr Glu Leu Pro Trp Trp Gly Lys Val Pro Arg Lys
      20           25           30
Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Xaa Asp Lys

```

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys  
 755 760 765  
 Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser  
 770 775 780  
 Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp  
 785 790 795 800  
 Arg Glu Val Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly  
 805 810 815  
 Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn  
 820 825 830  
 Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe  
 835 840 845  
 Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser  
 850 855 860  
 Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn  
 865 870 875 880  
 Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu  
 885 890 895  
 Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile  
 900 905 910  
 Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn  
 915 920 925  
 Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro  
 930 935 940  
 Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu  
 945 950 955 960  
 Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe  
 965 970 975  
 Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His  
 980 985 990  
 Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser  
 995 1000 1005  
 Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu  
 1010 1015 1020  
 Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His  
 1025 1030 1035 1040  
 Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met  
 1045 1050 1055  
 Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met  
 1060 1065 1070  
 Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys  
 1075 1080 1085  
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr  
 1090 1095 1100  
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys  
 1105 1110 1115 1120  
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp  
 1125 1130 1135  
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His  
 1140 1145 1150  
 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp  
 1155 1160 1165  
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg  
 1170 1175 1180  
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val  
 1185 1190 1195 1200  
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys  
 1205 1210 1215



Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile  
 355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys  
 370 375 380  
 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser  
 385 390 395 400  
 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys  
 405 410 415  
 Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly  
 420 425 430  
 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys  
 435 440 445  
 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly  
 450 455 460  
 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys  
 465 470 475 480  
 Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys  
 485 490 495  
 Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp  
 500 505 510  
 Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu  
 515 520 525  
 Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp  
 530 535 540  
 Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln  
 545 550 555 560  
 Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val  
 565 570 575  
 Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn  
 580 585 590  
 Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu  
 595 600 605  
 Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp  
 610 615 620  
 Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys  
 625 630 635 640  
 Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys  
 645 650 655  
 Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys  
 660 665 670  
 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala  
 675 680 685  
 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly  
 690 695 700  
 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser  
 705 710 715 720  
 Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser  
 725 730 735  
 His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln  
 740 745 750

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn  
 1685 1690 1695  
 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr  
 1700 1705 1710  
 Met Lys His Gln Ser Gln Leu  
 1715

<210> 379  
 <211> 656  
 <212> PRT  
 <213> Homo sapien

<400> 379  
 Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys  
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 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile

Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly  
 1220 1225 1230  
 Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn  
 1235 1240 1245  
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys  
 1250 1255 1260  
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro  
 1265 1270 1275 1280  
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr  
 1285 1290 1295  
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp  
 1300 1305 1310  
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val  
 1315 1320 1325  
 His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala  
 1330 1335 1340  
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala  
 1345 1350 1355 1360  
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn  
 1365 1370 1375  
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr  
 1380 1385 1390  
 Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr  
 1395 1400 1405  
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu  
 1410 1415 1420  
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly  
 1425 1430 1435 1440  
 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn  
 1445 1450 1455  
 Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser  
 1460 1465 1470  
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly  
 1475 1480 1485  
 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu  
 1490 1495 1500  
 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys  
 1505 1510 1515 1520  
 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser  
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 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu  
 1540 1545 1550  
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser  
 1555 1560 1565  
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe  
 1570 1575 1580  
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe  
 1585 1590 1595 1600  
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly  
 1605 1610 1615  
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro  
 1620 1625 1630  
 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln  
 1635 1640 1645  
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile  
 1650 1655 1660  
 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser  
 1665 1670 1675 1680

Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile  
 355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu  
 370 375 380  
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys  
 385 390 395 400  
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu  
 405 410 415  
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn  
 420 425 430  
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro  
 435 440 445  
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu  
 450 455 460  
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu  
 465 470 475 480  
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp  
 485 490 495  
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu  
 500 505 510  
 Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp  
 515 520 525  
 Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys  
 530 535 540  
 His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala  
 545 550 555 560  
 Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg  
 565 570 575

355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu  
 370 375 380  
 Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys  
 385 390 395 400  
 Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu  
 405 410 415  
 Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn  
 420 425 430  
 Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro  
 435 440 445  
 Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu  
 450 455 460  
 Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu  
 465 470 475 480  
 Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp  
 485 490 495  
 Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu  
 500 505 510  
 Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys  
 515 520 525  
 Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly  
 530 535 540  
 Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser  
 545 550 555 560  
 Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr  
 565 570 575  
 His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln  
 580 585 590  
 Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln  
 595 600 605  
 Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys  
 610 615 620  
 Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile  
 625 630 635 640  
 Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
 645 650 655

&lt;210&gt; 380

&lt;211&gt; 671

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 380

Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys  
 1 5 10 15  
 Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe  
 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110

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caaggtggac actctctaca gatcactgag gataagctgg agccacaatg catgaggcac 1680
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ctagataagg ccgtgagcag aaagaagggg aggatcctcc tatgttggtg aaggaggagc 1800
tagggggaga aactgaaagc tgattaatta caggagggtt gttcagggtc cccaaaccac 1860
cgtcagattt gatgatttcc tagcaggact tacagaaata aagagctatc atgctgtggt 1920
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aaagaagaat ccagaaatag gggcacattg aggaatgata ctgagcccaa agagcattca 2760
atcattggtt tatttgcctt cttttcacac cattggtgag ggagggatta ccacctggg 2820
gttatgaaga tgggtgaaca cccacacat agcaccggag atatgagatc aacagtttct 2880
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cccagctgat agaggaagta gccagggtgg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtttt 3279

```

&lt;210&gt; 383

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

```

Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
      5                                10                                15

```

```

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
      20                                25                                30

```

```

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
      35                                40                                45

```

```

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
      50                                55                                60

```

```

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
      65                                70                                75                                80

```

```

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
      85                                90                                95

```

```

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
      100                                105                                110

```

```

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
      115                                120                                125

```

Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His  
 580 585 590  
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn  
 595 600 605  
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile  
 610 615 620  
 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys  
 625 630 635 640  
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala  
 645 650 655  
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
 660 665 670

<210> 381  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 381

ggagaagcgt ctgctggggc aggaaggggt ttccctgccc tctcacctgt ccctcaccaa 60  
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 ccaatatccc aggagaagca ttggggaggt gggggcaggt gaaggacca ggactcacac 180  
 atcctggggc tccaaggcag aggagaggggt cctcaagaag gtcaggagga aaatccgtaa 240  
 caagcagtca g 251

<210> 382  
 <211> 3279  
 <212> DNA  
 <213> Homo sapiens

<400> 382

ctctctgcag ccccatgct ggtgaggggc acgggcagga acagtggacc caacatggaa 60  
 atgctggagg gtgtcaggaa gtgatcgggc tctggggcag ggaggagggg tggggagtg 120  
 cactgggagg ggacatcctg cagaaggtag gagttagcaa acaccgctg caggggaggg 180  
 gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggc ctgggaggg 240  
 gggcctggag ggcgtgagga ggagcgaggg ggctgcatgg ctggagttag ggatcagggg 300  
 cagggcgcga gatggcctca cacagggaag agagggcccc tctgcaggg cctcacctgg 360  
 gccacaggag gacactgott ttctctgag gagttaggag ctgtggatgg tgctggacag 420  
 aagaaggaca gggcctggct caggtgtcca gaggctgtcg ctggcttccc ttgggatca 480  
 gactgcaggg agggagggcg gcagggttgt ggggggagtg acgatgagga tgacctgggg 540  
 gtggctccag gccttgcgcc tgctggggc ctcaccagc ctccctcaca gtctcctggc 600  
 cctcagtctc tccctccac tccatcctcc atctggcctc agtgggtcat tctgatcact 660  
 gaactgacca taccagccc tgcccacggc cctccatggc tcccaatgc cctggagagg 720  
 ggacatctag tcagagagta gtctgaaga ggtggcctct gcgatgtgcc tgtgggggca 780  
 gcacatctga gatggtccc ggcctcatcc tgctgacctg tctgcaggga ctgtcctcct 840  
 ggaccttgcc ccttgtgcag gagctggacc ctgaagtccc ctcccatag gccaagactg 900  
 gagccttggt ccctctgttg gactccctgc ccatattctt gtgggagtggt gttctggaga 960  
 catttctgtc tgttctgag agctgggaat tgctctcagt catctgcctg cgcggttctg 1020  
 agagatggag ttgcctaggc agttattggg gccaatcttt ctcactgtgt ctctcctcct 1080  
 ttacccttag ggtgattctg ggggtccact tgtctgtaat ggtgtgcttc aaggtatcac 1140  
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 gcattaccgg aagtggatca aggacacat cgcagccaac cctgagtgcc cctgtccca 1260  
 cccctacctc tagtaaat t aagtccacct cacgttctgg catcacttgg ctttctgga 1320  
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 gacctgtgct ttctggtgtg gactccaggg ctgctaggaa aaggaatggg cagacacagg 1440  
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 ctctgaagac ttctcgctca gtttcagtga ggacacacac aaagacgtgg gtgacctgt 1560  
 tgtttgtggg gtgcagagat gggaggggtg gggcccaccc tggagagtg gacagtga 1620

```

tgaaccagga ccggtctctg ggcggtgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ccttttctc agcactgagg 240
gagggggctt gtttcccttc cctcccggcg acaagctcca ggcagggct gtccctctgg 300
gcggtccagc acttctcag acacaacttc ttctgtctgc tccagtcgtg gggatcatca 360
cttaccacc cccaagttc aagaccaa atctccagctg ccccttctg gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctgagcctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaaa aaaaaa 537

```

&lt;210&gt; 388

&lt;211&gt; 520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

```

aggataattt ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgaggttaaa ccagtttgca ttccccta atgtgaaaaag taagaggact actcagcact 120
gtttgaagat tgctcttct acagcttctg agaatttgtt tatttcaactt gccaaagtga 180
ggacccctc cccaacatgc ccagcccac ccctaagcat ggtccctgt caccaggcaa 240
ccaggaaact gctacttgtg gacctacca gagaccagga gggtttggt agctcacagg 300
acttccccca cccagaaga ttagcatccc atactagact cataactcaac tcaactagc 360
tcataactca ttgatggta ttagacaatt ccatttctt ctggttatta taaacagaaa 420
atctttctc ttctcattac cagtaaaggc tcttggtatc tttctgttg aatgatttct 480
atgaacttgt cttattttaa tggagggtt ttttctggt 520

```

&lt;210&gt; 389

&lt;211&gt; 365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

```

cgttgcccc gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctcccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcgtcctag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctcaccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ctttctctg ctticagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag 365

```

&lt;210&gt; 390

&lt;211&gt; 221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(221)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 390

```

tgctctcca tctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggnnt ctcatgggtg tggaacatct ctgcttgccg ttccaggaag gcctctggct 120
gctctangag tctgancga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

```

&lt;210&gt; 391

&lt;211&gt; 325

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens



Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn  
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu  
 145 150

<210> 384  
 <211> 557  
 <212> DNA  
 <213> Homo sapiens

<400> 384  
 ggatcctcta gagcgccgc ctactactac taaattcgcg gccgcgtcga cgaagaagag 60  
 aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120  
 ggggaagggt cccttttgca ttgccaagt ccataaccat gagcactact ctaccatggg 180  
 tctgcctcct ggccaagcag gctggtttgc aagaatgaaa tgaatgattc tacagctagg 240  
 acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300  
 ctctgtagag agcagcattc ccaggacact tggaaacagt tggcactgta aggtgcttgc 360  
 tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420  
 ctttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaaagt 480  
 tcaattgtga aaatgaatat catgcaata aattatgcga ttttttttc aaagtaaaaa 540  
 aaaaaaaaa aaaaaaa 557

<210> 385  
 <211> 337  
 <212> DNA  
 <213> Homo sapiens

<400> 385  
 ttcccagggt atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60  
 gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120  
 tctcaaagcc atctgctgtc ttcgagtacg gacacatcat cactcctgca ttgttgatca 180  
 aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240  
 tatcagacag gtccagtttc cgcaccaaca cctgctgggt ccctgtcgtg gtctggatct 300  
 ctttggccac caattcccc tttccacat cccggca 337

<210> 386  
 <211> 300  
 <212> DNA  
 <213> Homo sapiens

<400> 386  
 gggcccgtca ccggcccagg cccgcctcgc cgagtcctcc tccccgggtg cctgcccga 60  
 gcccgtcgcg ccagagggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120  
 gcgaccttgg ccgaaggct ctagcaagga cccaccgacc ccagccgcgg cggcgggcgc 180  
 gcggactttg cccggtgtgt ggggcggagc ggactgctg tccgcggacg ggcagcgaag 240  
 atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

<210> 387  
 <211> 537  
 <212> DNA  
 <213> Homo sapiens

<400> 387  
 gggccgagtc gggcaccaag ggactctttg caggcttctt tctcggatc atcaaggctg 60  
 cccctcctg tgccatcatg atcagcacct atgagttcgg caaaagcttc ttccagaggc 120

&lt;400&gt; 394

```

gaacatacat gtcccgccac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaatng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggacccaa ttaccattac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt 384

```

&lt;210&gt; 395

&lt;211&gt; 399

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 395

```

ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcattcatt cggaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttctct ttggaaagcc tgggcattct ctcactacag acctctgacc atgggacggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac 399

```

&lt;210&gt; 396

&lt;211&gt; 403

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(403)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 396

```

tggagtntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtggag gataaaagaa ggaaaaaaag aagagtgaga aaacctat 360
atcaaagcag gtgctatcac tcaatgtag gccctgctct ttt 403

```

&lt;210&gt; 397

&lt;211&gt; 100

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(100)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 397

```

actagtnacg tgtggtggaa ttcgcggccg cgtcgacctc naanccatct ctatagcaaa 60
tccatccccg ctctggttg gtnacagaat gactgacaaa 100

```

&lt;210&gt; 398

&lt;211&gt; 278

<220>  
 <221> misc\_feature  
 <222> (1)...(325)  
 <223> n = A,T,C or G

<400> 391  
 tggagcaggt cccgaggect ccctagagcc tggggccgac tctgtgncga tgcangcttt 60  
 ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120  
 tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180  
 naanttingat ntccanagcc ctaccatcn tagttctgct ctcccaccgg ntaccagccc 240  
 cactgcccag gaatcctaca gccagtaccc tgtcccgcag totctaccta ccagtacgat 300  
 gagacctccg gctactacta tgacc 325

<210> 392  
 <211> 277  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(277)  
 <223> n = A,T,C or G

<400> 392  
 atattgttta actccttctt ttatatcttt taacattttc atggngaaag gttcacatct 60  
 agtctcaact nggcnagn gnctcacttg agtctcttcc cgggcctgnn ccagtngnaa 120  
 antaccanga accgncatgn cttanaaen nccgtggttn tgggttnntc aatgactgca 180  
 tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240  
 ctgaggatac agcgcgcgt cctgtgttgc tggggaa 277

<210> 393  
 <211> 566  
 <212> DNA  
 <213> Homo sapiens

<400> 393  
 actagtcag tgtggtggaa ttccgcggccg cgtcgacgga caggtcagct gtctggctca 60  
 gtgatctaca ttctgaagtt gtctgaaaat gtcttcata ttaaattcag cctaaacggt 120  
 ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180  
 gagaaggctt agtttgtcca tcagcattat catgatata ggactgggta cttgggttaag 240  
 gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttgga 300  
 ggggtggttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360  
 catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420  
 ttctgcctca atgtttactg tgcctttgtt ttgtctagtt tgtgttgttg aaaaaaaaaa 480  
 cattctctgc ctgagtttta atttttgtcc aaagttattt taatctatac aattaaaagc 540  
 ttttgctat caaaaaaaaa aaaaaa 566

<210> 394  
 <211> 384  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(384)  
 <223> n = A,T,C or G

<400> 401  
actgtttcca tgttatgttt ctacacattg ctacctcagt gtccttgga acttagcttt 60  
tgatgtctcc aagtagtcca ctttcattta actctttgaa actgtatcat ctttgccaag 120  
taagagtggg ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180  
tataaatgaa tgtgctgaag caaagtgcc atggtggcgg cgaagaagan aaagatgtgt 240  
tttgttttg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300  
cccttttgca ttgccaagt ccataaccat gagcactact ctacatggn tctgc 355

<210> 402  
<211> 407  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(407)  
<223> n = A,T,C or G

<400> 402  
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60  
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120  
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180  
gaataaagat aaaaaagaga aggacattac aaagtggtc ctgacctttg ataaatctca 240  
ttgcttgata ccaacctggg ctgttttaat tgcccaaac aaaaggataa tttgctgagg 300  
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360  
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa 407

<210> 403  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 403  
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaatcc aggcaccaa 60  
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120  
tagagaacaa gacctactca gtcataaaca aaaaggcaga caccaacatg gatctcatgg 180  
gggattggat attgtaatta tagagcagga agatgacagt gatcgatcatt tggcacaaca 240  
tcttaacaac gaccgaaacc cattattttac ataaacctcc attcggtaac catgttgaaa 300  
gga 303

<210> 404  
<211> 225  
<212> DNA  
<213> Homo sapiens

<400> 404  
aagtgttaact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60  
attgttaatg cactcattta cttttacatg gtgaaagttc tctcttgatc ctacaaacag 120  
acattttcca ctcgtgttcc catagtgttt aagtgatca gatgtgttgg gcatgtgaat 180  
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcatt 225

<210> 405

<212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(278)  
 <223> n = A,T,C or G

<400> 398  
 ggggccgcgt cgacagcagt tccgccagcg ctgcgccctg ggtggggatg tgctgcacgc 60  
 ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120  
 tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgagggtg actcatcatg 180  
 ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240  
 ctatggccgc ttcattangt ggctcaacaa ggagaagg 278

<210> 399  
 <211> 298  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(298)  
 <223> n = A,T,C or G

<400> 399  
 acggaggtgg aggaagcgnc cctgggatcg anaggatggg tcctgncatt gaccncctcn 60  
 ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120  
 ccgagatcga ggcgatgggc ctggtcatgg accgatggg ctccgtggag cgcgatgggct 180  
 ccggcattga ggcgatgggc ccgctgggccc tcgaccacat ggccctccanc attganccga 240  
 tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcattggg 298

<210> 400  
 <211> 548  
 <212> DNA  
 <213> Homo sapiens

<400> 400  
 acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttctgcctt 60  
 gtacatgtac atgtatgaaa ttcccttctc ttaccgaact ctctccacac atcacaaggt 120  
 caaagaacca cagcgttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180  
 tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240  
 tgcagagggc tagagaatta ttcatatagc gctttgaggc caccatgtc acttatcccg 300  
 tataccctct caccatcccc ttgtctactc tgatgcccc aagatgcaac tgggcagcta 360  
 gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420  
 ctttccagtg atctcctacc atgggcccc ctccctggg caagccccctc ccaggccctg 480  
 tccccagccc ctctgcccc agcccacccg cttgccttgg tgctcagccc tcccattggg 540  
 agcaggtt 548

<210> 401  
 <211> 355  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(355)  
 <223> n = A,T,C or G

```

ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtcct ttgnnattaa 60
tnccttaacta gttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120
cattatcctt ccagtattcn ccttctnttt tatttactcc ttcttggtta cccatgtact 180
ntt 183

```

```

<210> 409
<211> 250
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(250)
<223> n = A,T,C or G

```

```

<400> 409
cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtgggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgtctacgg ccttatctag 180
gcttccagtg gccccagga cagcgtgggc tatgtttaca gcgntcctt gctggggggg 240
ggcctatgc 250

```

```

<210> 410
<211> 306
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(306)
<223> n = A,T,C or G

```

```

<400> 410
ggctgggttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tcccatttgc aggatccgtc tgtgcacatg cctctgtaga gaggcagcatt 120
cccagggaacc ttggaaacag ttggcactgt aagggtgctt ctcccccaaga cacatcctaa 180
aagggtgttg aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
tcntgc 306

```

```

<210> 411
<211> 261
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A,T,C or G

```

```

<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a 261

```

```

<210> 412

```

<211> 334  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(334)  
 <223> n = A,T,C or G

<400> 405  
 gagctgttat actgtgagtt ctactaggaa atcatcaa atgagggttg tctggaggac 60  
 ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120  
 tcatccccat cccatgccaa aggaagaccc tccctccttg gtcacagcc ttctctaggc 180  
 ttcccagtgct ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtg 240  
 ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300  
 cactctccac tctctcannig tggatcccac ccct 334

<210> 406  
 <211> 216  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(216)  
 <223> n = A,T,C or G

<400> 406  
 ttccatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60  
 gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120  
 acnaaacaca aattttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180  
 actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407  
 <211> 413  
 <212> DNA  
 <213> Homo sapiens

<400> 407  
 gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60  
 gtaaattgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120  
 gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaatt 180  
 cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240  
 ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atggggcaacc 300  
 tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360  
 tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag 413

<210> 408  
 <211> 183  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(183)  
 <223> n = A,T,C or G

<400> 408

<210> 416  
<211> 213  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(213)  
<223> n = A,T,C or G

<400> 416  
atgcataatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60  
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120  
cgaatgcaag gtgggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180  
atattggaac agatggagtc tctactacaa aag 213

<210> 417  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 417  
nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60  
gtgggaaagg ctttactctg agttcaaata ttcaagccca tcagagagtc cacactggag 120  
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180  
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240  
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300  
agt 303

<210> 418  
<211> 328  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(328)  
<223> n = A,T,C or G

<400> 418  
tttttgccgg tgggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60  
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120  
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180  
gtatttttag tagagacagg gtttcacat gttggccagg ctggtctcaa actcctnacc 240  
tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300  
aaagtgctan gattacaggc cgtgagcc 328

<210> 419  
<211> 389  
<212> DNA  
<213> Homo sapiens



<211> 241  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(241)  
 <223> n = A,T,C or G

<400> 412  
 gttcaatggt acctgacatt tctacaacac cccactcacc gatgtattcg ttgccagtg 60  
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgccagg aaatactacg 120  
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180  
 ctgggagatt tctactggga cattgaattc ccaaactacc cangcaatta cccagccaac 240  
 a 241

<210> 413  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(231)  
 <223> n = A,T,C or G

<400> 413  
 aactcttaca atccaagtga ctcatctgtg tgcttgaatc cttccactg tctcatctcc 60  
 ctcatccaag tttctagtag cttctctttg ttgtgaagga taatcaaaact gaacaacaaa 120  
 aagtttactc tcctcatttg gaacctaaaa actctcttct tctgggtct gagggctcca 180  
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414  
 <211> 234  
 <212> DNA  
 <213> Homo sapiens

<400> 414  
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60  
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120  
 gtgagccaag gagggagggt cttccttttg catgggatgg ggatgaagta aggagaggga 180  
 ctggaccccc tggaaagctga ttactatgg ggggaggtgt attgaagtcc tcca 234

<210> 415  
 <211> 217  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(217)  
 <223> n = A,T,C or G

<400> 415  
 gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60  
 caaaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120  
 caccatgcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180  
 antggattat aaaaaataac aattaagaaa aataatc 217

<210> 423  
<211> 310  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(310)  
<223> n = A,T,C or G

<400> 423  
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60  
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120  
tcaactgacag aacaggtctt ttttgggtcc ttcttctcca ccacgatata cttgcagtcc 180  
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240  
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300  
tccgagttta 310

<210> 424  
<211> 370  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(370)  
<223> n = A,T,C or G

<400> 424  
gctcaaaaat ctttttactg atagggcatg ctacacaatc attgactatt agaggccaga 60  
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120  
cactgacaga acaggtcttt tttgggtcct tcttctccac cacgatatac ttgcagtcct 180  
ccttcttgaa gattcttttg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240  
ggttgaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300  
cacgaagggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360  
tccgtcgacg 370

<210> 425  
<211> 216  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(216)  
<223> n = A,T,C or G

<400> 425  
aattgctatn ntttattttg ccaactcaaaa taattaccaa aaaaaaaaaa tnttaaata 60  
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120  
anattatcca ttatnttaag ggttgacttc aggnacagc acacagacaa acatgcccag 180  
gaggntntca ggaccgctcg atgtntntg aggagg 216

<210> 426  
<211> 596  
<212> DNA  
<213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(389)  
 <223> n = A,T,C or G

<400> 419  
 cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60  
 acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120  
 cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180  
 cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggg gtgccaggca 240  
 ccggttctcc agccaccaac ctactcgct cccgcaaatg gcacatcagt tcttctaccc 300  
 taaaggtagg accaaagggc atctgctttt ctgaagtctt ctgctctatc agccatcacg 360  
 tggcagccac tcnngctgtg tcgacgcgg 389

<210> 420  
 <211> 408  
 <212> DNA  
 <213> Homo sapiens

<400> 420  
 gttcctccta actcctgcc aaacagctc tcctcaacat gagagctgca cccctcctcc 60  
 tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttcc tggctagacc 120  
 gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180  
 gtccattga cacctttcc actgaccca taaaggaatc ctcatggcca caaggatttg 240  
 gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300  
 gatatagaaa attcttgaat gagtcctata aacatgaaca ggtttatatt cgaagcacag 360  
 acgttgaccg gactttgatg aagtgcctatg acaaacctgg caagcccg 408

<210> 421  
 <211> 352  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(352)  
 <223> n = A,T,C or G

<400> 421  
 gctcaaaaat ctttttactg atnngcatgg ctacacaatc attgactatt acggaggcca 60  
 gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120  
 ttactgaca gaacaggtct ttttgggtc cttcttctcc accacnatat atttgagtc 180  
 ctcttcttg aagattcttt ggagttgtc tttgtcataa cccacaggtg tagaaacaag 240  
 ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300  
 cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg 352

<210> 422  
 <211> 337  
 <212> DNA  
 <213> Homo sapiens

<400> 422  
 atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60  
 cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120  
 gcgatagcaa ggtgcggcg atcgcgcgcg cgtcaatcct ggccaaggct agccgtgatc 180  
 gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggtc 240  
 atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300  
 gcttcttcgg ccggtacggc tggcctatga aaattat 337

<211> 507  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(507)  
 <223> n = A,T,C or G

<400> 430  
 cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60  
 gaacactgac acccatcttc caccocgaca ctctgattta attgggctgc agtgagaaca 120  
 gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttggt atctttgccn 180  
 ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240  
 attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300  
 caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360  
 tgtcagtga tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420  
 cattctctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480  
 ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431  
 <211> 392  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 431  
 gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60  
 aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120  
 tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180  
 aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtctggggtt ttccaacaga 240  
 catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300  
 acaaaagtga tgttgttagg taaaatgtac aacttctgga totatgcaga cattgaaggt 360  
 gcaatgagtc tggcttttac tctgctgttt ct 392

<210> 432  
 <211> 387  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(387)  
 <223> n = A,T,C or G

<400> 432  
 ggtatcncta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60  
 aaatgcaagg caacatgtgt agatctcttg tottattctt ttgtctataa tactgtattg 120  
 ngtagtccaa gctctcgna gtccagccac tngnaaacat gctcccttta gattaacctc 180  
 gtggacnctn ttgttgnatt gtctgaactg tagngccctg tatitttgctt ctgtctgnga 240  
 attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300  
 atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360  
 acaacgtata gaacactgga gtccttt 387

&lt;400&gt; 426

```

cttccagtga ggataaccct gttgccccgg gccgagggtc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gcccgaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggccca ttaagaggca cttcccgtta 300
ttaaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattgggt tactgcctga 540
gtcccgtggt tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596

```

&lt;210&gt; 427

&lt;211&gt; 107

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(107)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 427

```

gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccg ctcagng 107

```

&lt;210&gt; 428

&lt;211&gt; 38

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(38)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 428

```

gaacttccna anaangactt tattcactat tttacatt 38

```

&lt;210&gt; 429

&lt;211&gt; 544

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 429

```

ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatacat cggttttcag 180
tttgatggtt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcaactcacc atcctctcct gttggttctg tgctgcttca 300
agataactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccagggt gtaggagaga 544
ttat

```

&lt;210&gt; 430

&lt;400&gt; 436

```

accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagtctctg aaaacgaggg 180
cagtttctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacaggggt 300
gccaggtttg tcatagcact catcaaagtc cggccaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctataat tctttcttat atactctcca 420
agttcataat gctgctccat gccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaagggt tcaatgggac ttcgggtctcc atgccgaaac 540
accaaagtca caaacttcaa ctcttgggt agtacacttc ggtctagcca gaaaaaagg 600
agaaacaaga agccaagggt aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tggtgag

```

&lt;210&gt; 437

&lt;211&gt; 693

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 437

```

ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc acactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaaact tcagacagct ttttcagatc 180
ataaaagata attcttagcc catgttcttc tccagagcag acctgaaatg acagcacagc 240
aggtaactct ctattttcac cctcttgc tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttgggggggac agccagcatc tttagctttc 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaaact gctgttgctc ctgaggtggg gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc

```

&lt;210&gt; 438

&lt;211&gt; 360

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

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ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgaggagg ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctgggtg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360

```

&lt;210&gt; 439

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(431)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 439

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gttcctnnta actcctgcc aaacagctc tcctcaacat gagagctgca cccctcctcc 60

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<210> 433  
 <211> 281  
 <212> DNA  
 <213> Homo sapiens  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(281)  
 <223> n = A,T,C or G

<400> 433  
 ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60  
 ctgattaaag aacactaaga gagggaacaag gctagaagcc gcaggatgtc tacactatag 120  
 caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180  
 atcgccgtgg ctattcctcn ttgntattac accagnagg ntctctgtnt gccactggg 240  
 tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

<210> 434  
 <211> 484  
 <212> DNA  
 <213> Homo sapiens

<400> 434  
 ttttaaaata agcatttagt gctcagtcct tactgagtac tctttctctc ccctcctctg 60  
 aatttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatattg 120  
 tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtaa tccatcttgc 180  
 tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240  
 agctagtcta tcagcatctg acaggtgaat tggatgggtc tcagaacat ttcacccaga 300  
 cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360  
 tgtcccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420  
 tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480  
 tttta 484

<210> 435  
 <211> 424  
 <212> DNA  
 <213> Homo sapiens

<400> 435  
 ggcgcgtca gagcaggtca ctttctgcct tccaagtcct cttcaagga agcccatgt 60  
 gggtagcttt caatatcgca ggttccttact cctctgcctc tataagctca aaccaccaa 120  
 cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgag 180  
 atgggctgtt ggggagggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240  
 cttggagaga ggaaaaaggc cacaagaggg gctgccaccg cactaacgg agatggccct 300  
 ggtagagacc tttgggggtc tggaaacctc ggactcccca tgctctaact cccacactct 360  
 gctatcagaa acttaaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420  
 aaac 424

<210> 436  
 <211> 667  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(667)  
 <223> n = A,T,C or G

<220>  
<221> misc\_feature  
<222> (1)...(624)  
<223> n = A,T,C or G

<400> 443  
tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60  
ttgaaagaat taaattcaga ggaggggaga gaaagagtag tcagtaggga ctgagcacta 120  
aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180  
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240  
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaaacttg cttcctgttt 300  
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc tttaatgaac 360  
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420  
atggtaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaata 480  
agtacagaga gagggcactt aaaccaacta agggcctgga gggaagggtt cctggaaaga 540  
ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaaact 600  
ttgtccctat ctgctaaca gatc 624

<210> 444  
<211> 425  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(425)  
<223> n = A,T,C or G

<400> 444  
gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60  
gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120  
ttcattgcta tagcataaca caaaatttgc ataagtgtg gtcagcaaat ccttgaatgc 180  
tgcttaattgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240  
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300  
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcacacctg gaagagccaa 360  
ggaggcacca gggcataagt gagtagactt atggctcgacg cggccgcgaa tttagtagta 420  
gtaga 425

<210> 445  
<211> 414  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(414)  
<223> n = A,T,C or G

<400> 445  
catgtttatg nttttggatt actttgggca cctagtgttt ctaaactcgtc tatcattcct 60  
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatcct caagtctttg 120  
tgaaattctt tgcattgtgc agattatttg atgtagtttc ctttaactag catataaatc 180  
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240  
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300  
ggatttttat aatcctactc acaaatgact aggccttctc tcttgtattt tgaagcagtg 360  
tggtgtgtgg attgataaaa aaaaaaaaag tcgacgcggc cgcaattta gtag 414

<210> 446



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tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtccattga cacctttccc actgaccca taaaggaatc ctcatggcca caaggatttg 240
gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t 431

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&lt;210&gt; 440

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

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agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcttggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaac acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta 523

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&lt;210&gt; 441

&lt;211&gt; 430

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

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gttcctccta actcctgcc aagacagctc tctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtccattga cacctttccc actgaccca taaaggaatc ctcatggcca caaggatttg 240
gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtctata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag 430

```

&lt;210&gt; 442

&lt;211&gt; 362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

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ctaaggaatt agtagtggtt ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tgggtgggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgttttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc 362

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&lt;210&gt; 443

&lt;211&gt; 624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<210> 449  
<211> 706  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(706)  
<223> n = A,T,C or G

<400> 449  
ccaagttcat gctntgtgct ggacgctgga caggggggcaa aagcnnttgc tcgtgggtca 60  
ttctganacac cgaactgacc atgccagccc tgccgatggc cctccatggc tccctagtgc 120  
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180  
cggggacagc atcctgcaga tggtcgggag cgtcccatc gccattcagg ctgcgcaact 240  
gttggaagg gcgatcggtg cgggcctctt cgctattac ccagctggcg aaagggggat 300  
gtgctgcaag gcgattaat tgggtaacgc caggggtttc ccagtcncga cgttgtaaaa 360  
cgacggccag tgaattgaat ttagggtgacn ctatagaaga gctatgacgt cgcgtgcacg 420  
cgtaacgtaag cttggatcct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480  
cgacgtggga tccncaactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540  
cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600  
aacaggttga acctgggagg tggagggttc aatgagctga gatcaggccn ctgcncacca 660  
gcatggtatga cagagtgaata ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450  
<211> 493  
<212> DNA  
<213> Homo sapiens

<400> 450  
gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60  
acagtttttaa aaggtaaaaac aacataaaaa gaaatatcct atagtggaaa taagagagtc 120  
aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcaactgcatg 180  
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240  
caagtccagt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300  
agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360  
tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420  
tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480  
gcgaatttag tag 493

<210> 451  
<211> 501  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(501)  
<223> n = A,T,C or G

<400> 451  
gggcgcgtcc cattcgccat tcaggctgcg caactgttgg gaaggcgcat cgggtgcgggc 60  
ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120  
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180  
tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240  
gcggccgcct actactacta aattcgcggc cgcgtcgacg tgggatccnc actgagagag 300  
tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360  
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggagggtggag 420

<211> 631  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(631)  
<223> n = A,T,C or G

<400> 446  
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60  
tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcagggtgtg 120  
atgctgggta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttggtc 180  
ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240  
ctgtcatctg tgtgggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300  
actgagattt gtaaaccttc caaccttcca ggaaatgcc cagaagcaac agaattcaca 360  
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420  
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttggg ctacacaata 480  
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgcttg catttggtgtg 540  
aatctacacc aatgaaaaca tgtactacag ctatatattga ttatgtatgg atatatttga 600  
aatagtatac attgtcttga tgttttttct g 631

<210> 447  
<211> 585  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(585)  
<223> n = A,T,C or G

<400> 447  
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60  
cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120  
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180  
agttcctgaa aggcaggtat agcaactgat cttcagaaaag aggaactgtg tgcaccggga 240  
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggtcg 300  
ccagggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360  
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420  
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480  
attcctttat ggggtcagtg ggaaagggtg caatgggact tcggtctcca tgccgaaaca 540  
ccaaagtcac aaacttcaac tccttggtca gtacacttcg gtcta 585

<210> 448  
<211> 93  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(93)  
<223> n = A,T,C or G

<400> 448  
tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggcncctat 60  
ggctccctag tgcctggag agganggggc tag 93

<212> DNA  
 <213> Homo sapiens

<400> 456  
 ttggcaggta cccttacaaa gaagacacca taccttatgc gttattaggt ggaataatca 60  
 ttccattcag tattatcggt attattcttg gagaaaccct gtctgtttac tgtaaccttt 120  
 tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180  
 cctttttatt tgggtgcagct gctagtcagt ccctgactga cattgccaag t 231

<210> 457  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(231)  
 <223> n = A,T,C or G

<400> 457  
 cgagggtaccc aggggtctga aaatctctnn ttantagtc gatagcaaaa ttgttcatca 60  
 gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120  
 tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180  
 agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231

<210> 458  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<400> 458  
 aggtcttggt cccccactt ccaactccct ctactctctc taggactggg ctgggccaaag 60  
 agaagagggg tggtaggga agccgttgag acctgaagcc ccacctcta ccttccttca 120  
 acaccctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180  
 ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t 231

<210> 459  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<400> 459  
 ggtaccgagg ctcgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60  
 ccttcgcgaa acctgtggtg gccaccagt cctaaccgga caggacagag agacagagca 120  
 gccctgcaat gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180  
 actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231

<210> 460  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<400> 460  
 gcagggtataa catgctgcaa caacagatgt gactaggaac ggccggtgac atggggaggg 60  
 cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaa 120  
 cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180  
 gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a 231

gttgcaatga gctgagatca ggccnctgcn ccccgatg gatgacagag tgaaactcca 480  
tcttaaaaaa aaaaaaaaaa a 501

<210> 452  
<211> 51  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(51)  
<223> n = A,T,C or G

<400> 452  
agacggtttc accnttaca cnccttttag gatgggnntt ggggagcaag c 51

<210> 453  
<211> 317  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(317)  
<223> n = A,T,C or G

<400> 453  
tacatcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60  
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatgggtc tcagaaccat 120  
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggtc tctacatgca 180  
taacaaaccc tgtccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240  
cccaccaaac tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300  
taccatgtc tttatta 317

<210> 454  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 454  
ttcgaggtag aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60  
taagccacgc cagctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120  
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180  
cttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 455  
taccaaagag ggcataataa tcagtctcac agtaggggtc accatcctcc aagtgaaaaa 60  
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120  
gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180  
caaagaattt ctcatagcac agctcacaat acagggtcc tttctcctct a 231

<210> 456  
<211> 231

&lt;213&gt; Homo sapiens

&lt;400&gt; 466

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cagggtacctc tttccattgg atactgtgct agcaagcatg ctctccgggg tttttttaat 60
ggccttcgaa cagaacttgc cacataccca ggtataatag tttctaacaat ttgccagga 120
cctgtgcaat caaatattgt ggagaattcc ctagctggag aagtcacaaa gactataggc 180
aataatggag accagtccca caagatgaca accagtcggt gtgtgcggct g 231

```

&lt;210&gt; 467

&lt;211&gt; 311

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 467

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gtacaccctg gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg 60
tggtggcttt tctccttttt catcaagact cctcagcagg gagcccagac cagcctgcac 120
tgtgccttaa cagaaggctc tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct ctgcccaagc tcgtaatgag actatagcaa ggcggtctgt ggacgtcagt 240
tgtgacctgc tgggcctccc aatagactaa caggcagtgc cagttggacc caagagaaga 300
ctgcagcaga c 311

```

&lt;210&gt; 468

&lt;211&gt; 3112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 468

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cattgtgttg ggagaaaaac agaggggaga tttgtgtggc tgcagccgag ggagaccagg 60
aagatctgca tgggtgggaag gacctgatga tacagagttt gataggagac aattaaaggc 120
tggaaggcac tggatgcctg atgatgaagt ggactttcaa actggggcac tactgaaacg 180
atgggatggc cagagacaca ggagatgagt tggagcaagc tcaataacaa agtggttcaa 240
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&lt;210&gt; 469

&lt;211&gt; 2229

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 469

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<210> 475

<211> 2414

<212> DNA

<213> Homo sapiens

<220>

<221> unsure

<222> (33)

<223> n=A,T,C or G

<400> 475

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 aaaaaaaaaa aaaa 2414

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&lt;210&gt; 474

&lt;211&gt; 1594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

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His Tyr His Arg Asp Thr Asp Thr Arg Arg His His His Met Asp Thr
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Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr
      35      40      45

His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp
      50      55      60

His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr
      65      70      75      80

Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His
      85      90      95

Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr
      100      105      110

Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val
      115      120      125

Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln
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<400> 478
Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln
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Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr
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Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr
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His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr

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<210> 476  
<211> 3434  
<212> DNA  
<213> Homo sapiens

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Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val  
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<210> 480  
<211> 144  
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<213> Homo sapiens

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Val Gly Phe Leu Val Val Lys Arg Gln Thr Ile Gly Arg Leu Glu Arg  
35 40 45

Asp Phe Met Phe Lys Cys Arg Lys Gln Pro Gly Leu Pro Pro Ser Gly  
50 55 60

Leu Cys Leu Leu Trp Pro Trp Pro Asn Leu Glu Phe Gly Arg Arg Gln  
65 70 75 80

Asp Arg Leu Thr Trp Ser Ser Val Ser Val Ala Gly Val Cys Ala Cys  
85 90 95

Arg Ala Arg Pro Gly Trp Leu Gly Glu Gln Pro Ala Thr Ser Ala Gly  
100 105 110

Val Arg Leu Glu Gln Val Glu Gln Pro Pro Ala His Pro Leu Gln Glu  
115 120 125

Ala Gly Val Ala Arg Phe Pro Arg Pro Glu Trp Val Pro Pro Asn Gly  
130 135 140

<210> 481  
<211> 167  
<212> PRT  
<213> Homo sapiens

<400> 481  
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20 25 30



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 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65                      70                      75                      80  
 Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser  
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 His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp  
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 Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser  
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 Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr  
 35                      40                      45  
 His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr  
 50                      55                      60  
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65                      70                      75                      80  
 Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser  
 85                      90                      95  
 His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val  
 100                      105                      110  
 Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val  
 115                      120                      125  
 Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr  
 130                      135                      140  
 Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His  
 145                      150                      155                      160  
 Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala  
 165                      170                      175  
 Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp

171

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Leu Ser His Ser  
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<210> 491  
<211> 20  
<212> PRT  
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<223> Made in a lab  
  
<400> 491  
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Thr Gly Phe Thr  
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<210> 492  
<211> 20  
<212> PRT  
<213> Artificial Sequence  
  
<220>  
<223> Made in a lab  
  
<400> 492  
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1 5 10 15  
Leu Ala Ser Leu  
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<210> 493  
<211> 20  
<212> PRT  
<213> Artificial Sequence  
  
<220>  
<223> Made in a lab  
  
<400> 493  
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Lys Tyr Arg Gly  
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<210> 494  
<211> 20  
<212> PRT  
<213> Artificial Sequence  
  
<220>  
<223> Made in a lab  
  
<400> 494  
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Leu Met Ile Ser

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<212> PRT
<213> Homo sapiens
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Arg Ala Ser Trp Leu Pro Gly Gly Gly Pro Gln Ala Ile Leu Gly Arg
      35                      40                      45

Thr Leu Cys Ser Ser Ala Glu Ser Ser Gln Asp Cys His Pro Gly Gly
      50                      55                      60

Pro Ser Ile Ala Leu Ala Lys Pro Cys Arg Gly Val Trp Leu Leu Phe
      65                      70                      75                      80

Glu Pro Ala Trp Pro Pro Trp His Ala Arg Ala Pro Gly Ala Gly Thr
      85                      90                      95

Leu Leu Arg Val Cys Leu Ser Cys Leu Gly Cys His Leu Cys Gly Gly
      100                     105                     110

Ala Ser Gly Gly Gly Gly Pro Ala Thr Asn Leu Thr Gln Ser Arg Lys
      115                     120                     125
```

<210> 499  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 499  
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp  
 1 5 10 15  
 Ser Ala Phe Leu  
 20

<210> 500  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 500  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 1 5 10 15  
 Gly Ser Ile Val  
 20

<210> 501  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 501  
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met  
 1 5 10 15  
 Val Ser Ala Ala  
 20

<210> 502  
 <211> 414  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n=A,T,C or G

<400> 502  
 caccatggag acaggcctgc gctggctttt cctggctcgct gtgctcaaag gtgtccaatg 60  
 tcagtcgggtg gaggagtccg ggggtcgcct ggtcacgcct gggacacctt tgacantcac 120  
 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccagggtcc 180  
 agggaagggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240

172

20

<210> 495  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 495  
 Asp Ser Leu Met Thr Ser Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro  
 1 5 10 15  
 Phe Pro Asn Gly  
 20

<210> 496  
 <211> 21  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 496  
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
 1 5 10 15  
 Pro Pro Pro Pro Ala  
 20

<210> 497  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 497  
 Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val  
 1 5 10 15  
 Ser Val Arg Val  
 20

<210> 498  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 498  
 Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala Arg Val  
 1 5 10 15  
 Val Pro Gly Arg  
 20

```

atggagacag gcctgcgtg gcttctcctg gtcgctgctc tcaaaggtgt ccagtgtcag    60
tcgctggagg agtccggggg tcgcctgggc acgcctggga caccctgac actcacctgc    120
accgtctctg gattctccct cagtagcaat gcaatgatct gggcccgcca ggctccaggg    180
aaggggctgg aatacatcgg atacattagt tatgggtgta gcgcatacta cgcgagctgg    240
gtgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatgaccagt    300
ctgacaaccg aggacacggc cacctatttc tgtgccagaa atagtgattt tagtggtatg    360
ttgtggggcc caggcacccct ggtcaccgtc tcctcagggc aacctaa                407

```

<210> 507  
 <211> 422  
 <212> DNA  
 <213> Homo Sapien

```

<400> 507
atggagacag gcctgcgtg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag    60
tcgggtggagg agtccggggg tcgcctgggc acgcctggga caccctgac actcacctgt    120
acagtctctg gattctccct cagcaactac gacctgaact gggcccgcca ggctccaggg    180
aaggggctgg aatggatcgg gatcattaat tatgttggtg ggacgggacta cgcgaactgg    240
gcaaaaaggcc gggtcaccat ctccaaaacc tcgaccacgg tggatctcaa gatcgccagt    300
ccgacaaccg aggacacggc cacctatttc tgtgccagag ggtggaagtg cgatgagtct    360
gggtcgtgct tgcgcattct gggcccaggc accctgggtc cgtctcctt agggcaacct    422
aa

```

<210> 508  
 <211> 411  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(411)  
 <223> n=A,T,C or G

```

<400> 508
atggagacag gcctgcgtgg cttctcctgg tcgctgtgct caaaggtgtc cagtgtcagt    60
cggtggagga gtccgggggt cgctgggtca cgcctgggac acccctgaca ctcacctgca    120
cagtctctgg aatcgacctc agtagctact gcatgagctg ggtccgcca gctccagggg    180
aggggctgga atggatcgga atcattggtg ctctgggtga cacatactac gcgaggtggg    240
cgaaaggccg attcaccatc tccaaaacct cgaccacggg gcatntgaaa atcnccagtc    300
cgacaaccga ggacacggcc acctatttct gtgccagaga tcttcgggat ggtagtagta    360
ctggttatta taaaatctgg ggcccaggca ccctgggtcac cgtctccttg g                411

```

<210> 509  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

```

<400> 509
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 1             5             10             15

```

<210> 510  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

gaaaggcoga ttnatnat ttt ccaaaacctn gaccacgggtg gatttgaaaa tgaccagtcc 300  
 gacaaccgag gacacggcca cctatttttg tggcagaatg aatactggta atagtgggtg 360  
 gaagaatatt tggggcccag gcaccctggt caccgtntcc tcagggaac ctaa 414

<210> 503  
 <211> 379  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(379)  
 <223> n=A,T,C or G

<400> 503  
 atncgatggt gcttgggtcaa aggtgtccag tgtcagtcgg tggaggagtc cgggggtcgc 60  
 ctgggtcacgc ctgggacacc cctgacactc acctgcaccg tntctggatt ngacatcagt 120  
 agctatggag tgagctgggt ccgccaggct ccagggaagg ggctgggnata catcggatca 180  
 ttagtagtag tggtagattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240  
 cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccaccatt 300  
 tntgtgccag aggggggttt aattataaag acatttgggg cccaggcacc ctggtcaccg 360  
 tntccttagg gcaacctaa 379

<210> 504  
 <211> 19  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 504  
 Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu  
 1 5 10 15  
 Asn Ser Ala

<210> 505  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 505  
 Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr  
 1 5 10 15  
 Asn Thr Ala Asn  
 20

<210> 506  
 <211> 407  
 <212> DNA  
 <213> Homo Sapien

<400> 506

<211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 515  
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg  
 1 5 10 15

<210> 516  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 516  
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln  
 1 5 10 15

<210> 517  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 517  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met  
 1 5 10 15

<210> 518  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 518  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly  
 1 5 10 15

<210> 519  
 <211> 17  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 519  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys  
 1 5 10 15



&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 510

Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile
1				5					10					15

&lt;210&gt; 511

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 511

Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gly	Gln	Asp	Gln	Lys
1				5					10					15

&lt;210&gt; 512

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 512

Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu
1				5					10					15

&lt;210&gt; 513

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 513

Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Asx	Val	Tyr	Thr	Asn	Leu
1				5					10					15

&lt;210&gt; 514

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 514

Leu	Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser
1				5					10					15

&lt;210&gt; 515

&lt;210&gt; 527

&lt;211&gt; 320

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 527

Met Ser Ser Cys Asn Phe Thr His Ala Thr Phe Val Leu Ile Gly Ile  
                                   5                                   10                                   15

Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser  
                                   20                                   25                                   30

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val  
                                   35                                   40                                   45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met  
                                   50                                   55                                   60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile  
                                   65                                   70                                   75                                   80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys  
                                   85                                   90                                   95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr  
                                   100                                   105                                   110

Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro  
                                   115                                   120                                   125

Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly  
                                   130                                   135                                   140

Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu  
                                   145                                   150                                   155                                   160

Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser  
                                   165                                   170                                   175

Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu  
                                   180                                   185                                   190

Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val  
                                   195                                   200                                   205

Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val  
                                   210                                   215                                   220

Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys  
                                   225                                   230                                   235                                   240

Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly  
                                   245                                   250                                   255

Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg  
                                   260                                   265                                   270

Gly

<210> 520  
<211> 25  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 520  
Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
1 5 10 15  
Glu Ala Arg Arg His Tyr Asp Glu Gly  
20 25

<210> 521  
<211> 21  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 521  
Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
1 5 10 15  
Pro Pro Pro Pro Ala  
20

<210> 522  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 522  
Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp  
1 5 10 15  
Phe Thr Gln Val  
20

<210> 523  
<211> 254  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<220>  
<221> VARIANT  
<222> (1)...(254)  
<223> Xaa = any amino acid

&lt;400&gt; 523

```

Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile
 1           5           10           15
Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile
          20           25           30
Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu
          35           40           45
Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln
 50           55           60
Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly
65           70           75           80
Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met
          85           90           95
Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu
          100          105          110
Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu
          115          120          125
Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala
          130          135          140
Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg
145          150          155          160
Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu
          165          170          175
Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys
          180          185          190
Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly
          195          200          205
Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly
          210          215          220
Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu
225          230          235          240
Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
          245          250

```

&lt;210&gt; 524

&lt;211&gt; 765

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 524

```

atggccacag caggaaatcc ctggggctgg ttctgggggt acctcatcct tgggtgtcgca      60
ggatcgctcg tctctggtag ctgcagccaa atcataaacg gcgaggactg cagcccgcac      120
tcgcagccct ggcaggcggc actggtcatg gaaaacgaat tgttctgctc gggcgctcctg      180
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg      240
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggg ggaggccagc      300
ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc      360
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag      420
tgccctaccg cggggaactc ttgcctcggt tctggctggg gtctgctggc gaacggcaga      480
atgcctaccg tgctgcagtg cgtgaacgtg tctgggtgtg ctgaggaggt ctgcagtaag      540
ctctatgacc cgctgtacca cccagcatg ttctgcgccc gcgaggaggca agaccagaag      600
gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt      660
gtgtctttcg gaaaagcccc gtgtggccaa gttggcgtgc cagggtgtcta caccaacctc      720
tgcaaatcca ctgagtggat agagaaaacc gtccaggcca gttaa      765

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&lt;210&gt; 525

&lt;211&gt; 254

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro  
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala  
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys  
305 310 315 320

<210> 528

<211> 20

<212> DNA

<213> Homo Sapien

<400> 528

actatggtcc agaggctgtg

20

<210> 529

<211> 20

<212> DNA

<213> Homo Sapien

<400> 529

atcacctatg tgccgcctct

20

<210> 530

<211> 1852

<212> DNA

<213> Homo sapiens

<400> 530

ggcacgagaa ttaaaaccct cagcaaaaca ggcatagaag ggacatacct taaagtaata 60  
 aaaaccacct atgacaagcc cacagccaac ataatactaa atggggaaaa gttagaagca 120  
 tttcctctga gaactgcaac aataaatata aggatgctgg attttgtcaa atgccttttc 180  
 tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat 240  
 ttattgactt gcctgtgtta gaccggaaga gctgggggtg ttctcaggag ccaccgtgtg 300  
 ctgcggcagc ttcgggataa cttgaggctg catcactggg gaagaaacac aytccgtgtc 360  
 gtggcgctga tggctgagga cagagcttca gtgtggcttc tctgcgactg gcttcttcgg 420  
 ggagtcttcc cttcatagtt catccatatg gctccagagg aaaattatat tattttgtta 480  
 tggatgaaga gtattacgtt gtgcagatat actgcagtgt cttcatctct tgatgtgtga 540  
 ttgggtaggt tccaccatgt tgccgcagat gacatgattt cagtacctgt gtctggctga 600  
 aaagtgtttg tttgtgaatg gatattgtgg tttctggatc tcatcctctg tgggtggaca 660  
 gctttctcca ccttgctgga agtgacctgc tgtccagaag tttgatggct gaggagtata 720  
 ccatcgtgca tgcacttttc atttctgca tttcttcctc cctggatgga cagggggagc 780  
 ggcaagagca acgtgggcac ttctggagac cacaacgact cctctgtgaa gacgcttggg 840  
 agcaagaggt gcaagtgggt ctgccactgc ttcccctgct gcagggggag cggaagagc 900  
 aacgtgggtc cttggggaga ctacgatgac agcgccttca tggatcccag gtaccacgtc 960  
 catggagaag atctggacaa gctccacaga gctgcctggt ggggtaaagt cccagaaaag 1020  
 gatctcatcg tcatgctcag ggacacggat gtgaacaaga gggacaagca aaagaggact 1080  
 gctctacatc tggcctctgc caatgggaat tcagaagtag taaaactcgt gctggacaga 1140  
 cgatgtcaac ttaatgtcct tgacaacaaa aagaggacag ctctgacaaa ggccgtacaa 1200  
 tgccaggaag atgaatgtgc gttaatgttg ctggaacatg gcactgatcc aaatattcca 1260  
 gatgagtatg gaaataccac tctacactat gctgtctaca atgaagataa attaatggcc 1320  
 aaagcactgc tcttatacgg tgctgatatc gaatcaaaaa acaagcatgg cctcacacca 1380  
 ctgctacttg gtatacatga gcaaaaacag caagtgtgta aatttttaaa caagaaaaaa 1440  
 gcgaatttaa atgcgctgga tagatatgga agaactgctc tcatacttgc tgtatgttgt 1500  
 ggatcagcaa gtatagtcag ccctctactt gagcaaaatg ttgatgtatc ttctcaagat 1560  
 ctggaaagac ggccagagag tatgctgttt ctagtcatca tcatgtaatt tgccagttac 1620

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tttctgacta caaagaaaaa cagatgttaa aaatctcttc tgaaaacagc aatccagaac 1680
aagacttaaa gctgacatca gaggaagagt cacaaaggct taaaggaagt gaaaacagcc 1740
agccagagct agaagattta tggctattga agaagaatga agaacacgga agtactcatg 1800
tgggattccc agaaaacctg actaacggtg ccgctgctgg caatggtgat ga 1852

```

<210> 531  
 <211> 879  
 <212> DNA  
 <213> Homo sapiens

```

<400> 531
atgcatcttt catttcctgc atttcttcct ccctggatgg acagggggag cggcaagagc 60
aacgtgggca cttctggaga ccacaacgac tcctctgtga agacgcttgg gagcaagagg 120
tgcaagtggg gctgccactg cttcccctgc tgcaggggga gcggcaagag caacgtgggc 180
gcttggggag actacgatga cagcgccttc atggatccca ggtaccacgt ccatggagaa 240
gatctggaca agctccacag agctgcctgg tggggtaaag tcccagaaa ggatctcatc 300
gtcatgtcca gggacacgga tgtgaacaag agggacaagc aaaagaggac tgctctacat 360
ctggcctctg ccaatgggaa ttcagaagta gtaaaactcg tgctggacag acgatgtcaa 420
cttaatgtcc ttgacaacaa aaagaggaca gctctgacaa aggccgtaca atgccaggaa 480
gatgaatgtg cgtaaatgtt gctggaacat ggcactgatc caaatattcc agatgagtat 540
ggaaatacca ctctacacta tgctgtctac aatgaagata aattaatggc caaagcactg 600
ctcttatacg gtgctgatat cgaatcaaaa aacaagcatg gcctcacacc actgctactt 660
ggtatacatg agcaaaaaca gcaagtgggtg aaatttttaa tcaagaaaaa agcgaattta 720
aatgcgctgg atagatatgg aagaactgct ctcatatttg ctgtatgttg tggatcagca 780
agtatagtca gccctctact tgagcaaaat gttgatgtat cttctcaaga tctggaaaga 840
cggccagaga gtatgctgtt tctagtcatc atcatgtaa 879

```

<210> 532  
 <211> 292  
 <212> PRT  
 <213> Homo sapiens

```

<400> 532
Met His Leu Ser Phe Pro Ala Phe Leu Pro Pro Trp Met Asp Arg Gly
      5                                10                                15

Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp His Asn Asp Ser Ser
      20                                25                                30

Val Lys Thr Leu Gly Ser Lys Arg Cys Lys Trp Cys Cys His Cys Phe
      35                                40                                45

Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val Val Ala Trp Gly Asp
      50                                55                                60

Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr His Val His Gly Glu
      65                                70                                75                                80

Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg
      85                                90                                95

Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Arg Asp
      100                                105                                110

Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser
      115                                120                                125

Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys Gln Leu Asn Val Leu

```

130                      135                      140  
 Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala Val Gln Cys Gln Glu  
 145                      150                      155                      160  
 Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile  
 165                      170                      175  
 Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Val Tyr Asn Glu  
 180                      185                      190  
 Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu  
 195                      200                      205  
 Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Ile His Glu  
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&lt;211&gt; 1228

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 537

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Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn  
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Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp  
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Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly  
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His Met Ile Tyr Arg Lys Ala Leu Arg Leu Ser Asn Met Ala Met Gly	130		135		140
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Ala Ser Arg Val Phe Val Ala Val Thr Leu Tyr Gly Ala Val Arg Leu	305		310		315
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Glu Lys Glu Ala Pro Trp Glu Tyr Gln Lys Arg Pro Pro Pro Ala Trp		
	980	985 990
Pro His Glu Gly Val Ile Ile Phe Asp Asn Val Asn Phe Met Tyr Ser		
	995	1000 1005
Pro Gly Gly Pro Leu Val Leu Lys His Leu Thr Ala Leu Ile Lys Ser		
	1010	1015 1020
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Lys Met Ser Ile Ile Pro Gln Glu Pro Val Leu Phe Thr Gly Thr Met		
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Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser Asn Phe Ser Val		
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Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala Asn Val Asp Pro Arg Thr		
	1155	1160 1165
Asp Glu Leu Ile Gln Lys Lys Ile Arg Glu Lys Phe Ala His Cys Thr		
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&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 553

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Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys
          5                      10                      15

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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
          20                      25                      30

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Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
          35                      40                      45

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Glu Pro His His Thr Gly Gly Gly Glu His
          50                      55

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<210> 554  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 554  
 Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile  
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 Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val  
                           20                          25                          30  
 Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro  
                           35                          40                          45  
 Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu  
                           50                          55

<210> 555  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<400> 555  
 Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln  
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 Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser  
                           20                          25                          30  
 Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp  
                           35                          40                          45  
 Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro  
                           50                          55                          60  
 Ser Asp Pro Leu Glu Leu Leu  
                           65                          70

<210> 556  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 556  
 Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr  
                           5                          10                          15  
 Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr  
                           20                          25                          30  
 Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly  
                           35                          40                          45  
 Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

203

50                      55                      60  
 Arg Asn Ser Leu Glu His Glu Pro Cys Cys Glu Leu Pro Ile Arg Arg  
   65                      70                      75                      80  
 Ile

<210> 557  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<400> 557  
 Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu  
                                   5                      10                      15

Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu  
                                   20                      25                      30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys  
                                   35                      40                      45

Gly Phe His Ile Arg Phe  
                                   50

<210> 558  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(77)  
 <223> Xaa = Any amino acid

<400> 558  
 Asn Asp Arg Asp Arg Asn Ser Asn Lys Val Ile Xaa Lys Ala Asn Leu  
                                   5                      10                      15

Ile Tyr Phe Thr Asn Leu Thr Ser Cys Leu Ser Val Gln Asn Gln Thr  
                                   20                      25                      30

Phe Thr Cys Thr Lys Arg His Lys His Leu Gln Cys Ser Ser Val His  
                                   35                      40                      45

Leu Cys Lys Ile Pro Pro Arg Leu Lys Gly Arg Asp Lys Lys Lys Lys  
                                   50                      55                      60

Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr  
                                   65                      70                      75

<210> 559  
 <211> 50  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 559

Thr Leu Pro Pro Leu Arg Ser Val Ile Thr Leu Glu Thr His Trp Ser  
                             5                            10                            15

Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala  
                             20                            25                            30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala  
                             35                            40                            45

Pro Arg  
           50

&lt;210&gt; 560

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly  
                             5                            10                            15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr  
                             20                            25                            30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn  
                             35                            40                            45

Thr Asp Leu Phe Leu Pro Pro Leu  
           50                            55

&lt;210&gt; 561

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(57)

&lt;223&gt; Xaa = Any amino acid

&lt;400&gt; 561

Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys  
                             5                            10                            15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser  
                             20                            25                            30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn  
                             35                            40                            45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn  
           50                            55

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<220>  
<221> VARIANT  
<222> (1)...(59)  
<223> Xaa = Any amino acid
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<400> 562
Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val
          5                      10                      15

Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
          20                      25                      30

Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
          35                      40                      45

Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
          50                      55

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<210> 563
<211> 79
<212> PRT
<213> Homo sapiens
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<400> 563  
Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro  
          5                      10                      15  
  
Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His  
          20                      25                      30  
  
Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met  
          35                      40                      45  
  
Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg  
          50                      55                      60  
  
Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg  
          65                      70                      75
```

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<210> 564
<211> 64
<212> PRT
<213> Homo sapiens
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<400> 564  
Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala  
                  5                  10                  15  
Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr  
                  20                  25                  30

Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser  
                   35                                  40                                  45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro  
                   50                                  55                                  60

<210> 565  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(57)  
 <223> Xaa = Any amino acid

<400> 565  
 Leu Tyr Tyr Cys Ser Tyr Leu Cys His Phe Arg Thr Ala Leu Ile Leu  
                                   5                                  10                                  15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln  
                                   20                                  25                                  30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu  
                   35                                  40                                  45

Tyr Ala Val Ser Ser Xaa His Asn Val  
                   50                                  55

<210> 566  
 <211> 55  
 <212> PRT  
 <213> Homo sapiens

<400> 566  
 Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg  
                                   5                                  10                                  15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His  
                   20                                  25                                  30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro  
                   35                                  40                                  45

Leu Lys Leu Val Leu Leu Pro  
                   50                                  55

<210> 567  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 567  
 Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu

5 10 15  
 Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile  
 20 25 30  
 Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile  
 35 40 45  
 Phe Arg Thr  
 50

<210> 568  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<400> 568  
 Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile  
 5 10 15  
 Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu  
 20 25 30  
 Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr  
 35 40 45  
 Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp  
 50 55 60  
 Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu  
 65 70 75

<210> 569  
 <211> 4809  
 <212> DNA  
 <213> Homo sapiens

<400> 569  
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 ggacagatgt ccgataatcc tttttacatt ttggcatcct tgggtagctc gtcttgtagg 180  
 aatggacttg cttcaaagtg gaggcaggca gatccttcag acgggtatat ggagccctgt 240  
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 ggtctgtagc acccagcaaa gtgctcagta aatgcgcagt aattgatttg acctctgaac 480  
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 ctacagggtg cacgcttggc atcacacatg tgccctgtgta ttcctctagg tggttaccag 600  
 gagctctgcc actgcatgct cactagtgcagggttcgctc caccacccca gctgggtagc 660  
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 acttctcaag agctaagaag gtttgctgag tattctggca tgatgtttgg tgatcaaaaca 780  
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actttgaaat	agttgtaaga	gttaagaaaa	agcacaaaa	tgagatcatc	agagcagctt	1860
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aaaaaaaaa 4809

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&lt;210&gt; 570

&lt;211&gt; 951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

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&lt;210&gt; 571

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 571

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aaataaacia acaaacaaac aaaacagaga gattttgct 819

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&lt;210&gt; 572

&lt;211&gt; 203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

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tatagaatac tcaagctatg catcaagctt ggtaccgagc tcggatccac tatttacggc 60

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210

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 atcaggtctc atgagaactc atg 203

<210> 573  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 573  
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 Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg  
                             20                            25                            30  
 Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu  
                             35                            40                            45  
 Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu  
                             50                            55                            60  
 Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala  
                             65                            70                            75                            80  
 Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly  
                             85                            90                            95  
 Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro  
                             100                            105                            110  
 Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile  
                             115                            120                            125  
 Leu Leu Asn Tyr  
                             130

<210> 574  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<400> 574  
 Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn  
                             5                            10                            15  
 His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln  
                             20                            25                            30  
 Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu  
                             35                            40                            45  
 Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala  
                             50                            55                            60

<210> 575

211

<211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
 Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp  
                           5                          10                          15  
 Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
                           20                          25                          30  
 Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                           35                          40                          45  
 Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                           50                          55                          60  
 Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
                           65                          70                          75

<210> 576  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(68)  
 <223> Xaa = Any Amino Acid

<400> 576  
 Met Leu Gly Lys Ser Arg Ala Val Cys Leu Pro Ser Thr Thr Val Thr  
                           5                          10                          15  
 Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr  
                           20                          25                          30  
 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln  
                           35                          40                          45  
 Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn  
                           50                          55                          60  
 Pro Gly Tyr Ser  
 65

<210> 577  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 577  
 Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg  
                           5                          10                          15  
 Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro

212

20                      25                      30  
 Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe  
                     35                      40                      45  
 Arg Leu Ala Pro Pro Ala Asp Thr Pro  
                     50                      55

<210> 578  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 578  
 Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His  
                                     5                      10                      15  
 His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr  
                                     20                      25                      30  
 Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr  
                                     35                      40                      45  
 Gln Pro His  
                     50

<210> 579  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 579  
 Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu  
                                     5                      10                      15  
 Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr  
                                     20                      25                      30  
 Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His  
                                     35                      40                      45  
 Ile Ala Lys Val Tyr Gln Pro His  
                     50                      55

<210> 580  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<400> 580  
 Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser  
                                     5                      10                      15  
 Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys  
                                     20                      25                      30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser  
                   35                                  40                                  45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser  
           50                                  55                                  60

Phe Ile His  
       65

<210> 581

<211> 77

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu  
                                   5                                  10                                  15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser  
                   20                                  25                                  30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala  
           35                                  40                                  45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu  
           50                                  55                                  60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser  
       65                                  70                                  75

<210> 582

<211> 51

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile  
                                   5                                  10                                  15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val  
                   20                                  25                                  30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe  
           35                                  40                                  45

Leu Gly Val  
       50

<210> 583

<211> 60

<212> PRT

<213> Homo sapiens

<400> 583

214

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                   5                  10                  15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                   20                  25                  30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
           35                  40                  45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
       50                  55                  60

&lt;210&gt; 584

&lt;211&gt; 76

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 584

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                   5                  10                  15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
           20                  25                  30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
           35                  40                  45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
       50                  55                  60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
       65                  70                  75

&lt;210&gt; 585

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 585

Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu  
                   5                  10                  15

Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp  
           20                  25                  30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu  
           35                  40                  45

Leu Phe  
       50

&lt;210&gt; 586

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys  
20 25 30

```
<210> 589
<211> 157
<212> PRT
<213> Homo sapiens
```

<400> 589  
Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met  
5 10 15

Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu  
20 25 30

Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu  
35 40 45

Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro  
50 55 60

Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg  
65 70 75 80

Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile  
85 90 95

Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser  
100 105 110

Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp  
115 120 125

Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly  
130 135 140

Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn  
145                      150                      155

```
<210> 590
<211> 347
<212> PRT
<213> Homo sapiens
```

<400> 590  
Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr  
5 10 15

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr  
 20 25 30  
 Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys  
 35 40 45  
 Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys  
 50 55 60  
 Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly  
 65 70 75 80  
 Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln  
 85 90 95  
 Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala  
 100 105 110  
 Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser  
 115 120 125  
 Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys  
 130 135 140  
 Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser  
 145 150 155 160  
 Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp  
 165 170 175  
 Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile  
 180 185 190  
 Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr  
 195 200 205  
 Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala  
 210 215 220  
 Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu  
 225 230 235 240  
 His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn  
 245 250 255  
 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His  
 260 265 270  
 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val  
 275 280 285  
 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile  
 290 295 300  
 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg  
 305 310 315 320



218

Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser  
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile  
 340 345

<210> 591  
 <211> 565  
 <212> DNA  
 <213> Homo sapien

<400> 591  
 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60  
 cttcatgcct tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120  
 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180  
 caggaagcaa gagttaatcc cagaggtcta tgtcctaattg tgttatggca aatggatgtc 240  
 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagtiga tacttattca 300  
 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360  
 ttatcttggt ttcctgtcat gggagttcca gaaaaagtta aaacagacaa tgggccaggt 420  
 tactgtagta aagcatttca aaaattctta aatcagtgga aaattacaca tacaatagga 480  
 atttcttata attcccaagg acaggccata attgaaggaa ctaatagaac actcaaagct 540  
 caattggtta aacaaaaaaaa aaaaa 565

<210> 592  
 <211> 188  
 <212> PRT  
 <213> Homo sapien

<400> 592  
 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile  
 1 5 10 15  
 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu  
 20 25 30  
 Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln  
 35 40 45  
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg  
 50 55 60  
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val  
 65 70 75 80  
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val  
 85 90 95  
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser  
 100 105 110  
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly  
 115 120 125  
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys  
 130 135 140  
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly  
 145 150 155 160  
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg  
 165 170 175  
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys  
 180 185

<210> 593  
 <211> 271

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(271)  
 <223> n = A,T,C or G

<400> 593  
 actttatgtt cnagtgcana aancncctg gattgccacc ntactctcag ggctgtgant 60  
 tgtgcnccca nagcaacctg ggcacgcggg gacagggggg ccnacaattg agggagcggg 120  
 gtccctagct ggggtctata catgncnggg naagggcngc tgagtnccat nagcaaagga 180  
 nctagnatnt gcgggggtgc ggcctgggpc taccctttna agcatccntn gatccactcc 240  
 angaancng gggtagncag gtttnccaac a 271

<210> 594  
 <211> 376  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(376)  
 <223> n = A,T,C or G

<400> 594  
 cctttggggg nggggggaac ctttaccatt gtncccttt atttcatttg gttnggggtc 60  
 gcgcctcnn gggccaacaa agttatcgtn nttgaagaga anattttttt ggnttngncc 120  
 cgattaagcg ncaaattgtgt agcaaaangc cgtgccactt gtggcgtagc tncgtcgggt 180  
 cgattcgacg acaaggcgtn gcgcgntanc gttagtctcn aatngaccn gtggcatgag 240  
 cccacgangg ntctgtgtcg tcacatggnc tctagacata acgcncncn ttttttncag 300  
 agggggntgc cgcccttagg gaggnagggg tggggacact agccaancca nantctnacc 360  
 ccattgaaga aaaggn 376

<210> 595  
 <211> 242  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(242)  
 <223> n = A,T,C or G

<400> 595  
 agnctgctgn tcgtnccctn tatgtggctt catnntgagg acaanagtng cactgagget 60  
 tgnnatgcc aggcaaggnc aagctggctc aaaaagcatc caccacctc tgnaangggg 120  
 atgccangag cangtgcacc agtcccaact angagnccn ggcatgntac atcttcttcc 180  
 acccctnaaa ntttngcta caangnccat ttttctttt ctcttaaggg ncnctggct 240  
 tc 242

<210> 596  
 <211> 535  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature

&lt;222&gt; (1)...(535)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 596

accagttgga	tactgctaaa	nagatatatta	tgcagcctca	tatgttaagt	cgtatatttt	60
gaaagctttt	taaatttttt	ctttaagaag	attttagatg	cttatcactg	agtaccagag	120
ggatgtaggc	tgatgccctt	atcaacaaag	tcagggactg	tggcacacaa	ggattgacta	180
ctgcagacac	ggccacaatg	ctacctctag	agggcctgaa	tccccctgcc	ctctctgggtg	240
gggagaaggg	ctggcagagc	cattagcatg	ggctccggcc	aatcctggcc	actttgacac	300
tcctgggtgct	gacccagggg	cctggaggaa	gggatgaggt	gggcagtaga	gatgctcagg	360
gcagtggccc	ctttccatcc	acactggaac	tatttcagta	ttttaccacc	aattcagcca	420
ttcccttggtg	cgctggctga	acatcagccc	tgctccaggt	ctcagtttcc	cctttgtaaa	480
gggaaagctc	tggattcagg	gagtgatgaa	gaggtcatca	tggtcttgag	aattc	535

&lt;210&gt; 597

&lt;211&gt; 257

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(257)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 597

tttcnatacc	caaaantacc	ccatattang	accanacatt	tgtctnggaa	aaattaccat	60
tnntaant	ttgggccacc	tgagannaaa	tggtgtaat	ncatgataag	atggancagn	120
attnctotta	agatnngatn	agaccccggt	tttcacggaa	catatccaag	nacccaatag	180
gnaacaagcc	acgggnggag	tcacaaacat	atattcttta	ctctcataat	ccgtnncaca	240
naactnttgn	acttgac					257

&lt;210&gt; 598

&lt;211&gt; 222

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(222)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 598

nntggntacc	gtcnaaactt	nncttggtac	ccgagctcgg	atccactagt	ccagtgtgggt	60
ggaattccat	tgtgttgggc	tataagctgt	aatagtggag	ncgtgctngg	ttcattgcan	120
nagnccctcc	gcanncacnc	ttggnacaac	ctgtgagnag	gcnataaatt	attcacataa	180
tcatcactgc	atgaanctga	ctcaaacgca	tccacntaca	cc		222

&lt;210&gt; 599

&lt;211&gt; 238

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(238)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 599

221

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnaggttt	ggtantgatc	tatgcaactc	catctcatgg	ggacgtttca	tgtggagtgn	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaaggggtca	tgtgaataca	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

&lt;210&gt; 600

&lt;211&gt; 232

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(232)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 600

cgaactat	ttt	agactaccta	ggaaaattat	tttagtatca	gaagaatata	aggggtgtag	60
tactcatcag	agctaaatga	gagcgcttta	aaaaatgtag	tttgtcttcc	gccatttcta		120
cagaaagctg	caatttcagg	ttttcaacct	aataggtgat	atttaanaaa	aaaaaaaagc		180
aatcgcaaat	agccccactg	cttttacaaa	tcattttttc	cccaacacaa	tg		232

&lt;210&gt; 601

&lt;211&gt; 547

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(547)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcca	ttgctttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaaattt	tttaaaaaga	240
catgtaatcc	gcgaggttag	taactcaaaa	cgagtgcata	tnggaagtat	cgcagccggt	300
nectgatnaa	attcccagct	tgctngcttg	ctnagccggg	gggcggtnaa	aaaaacatct	360
gcagcccnng	ggnaaaaacc	ttcgattgtg	tcttacgtgt	ttacgttatt	ttatttcctt	420
nnagcaaggc	nggganttg	ggactcgaaa	tggtacagtt	gggctgggga	tcgcccttgt	480
tacataaaaag	ncgtccagaa	gagggacggg	tacaggcngg	ganctccaaa	ggtcagtcct	540
tgccatt						547

&lt;210&gt; 602

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(826)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 602

cgggggggnnt	tacgtctctc	tggacgcttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttgct	ctagggaaat	aaaataacgt	aaacacgtaa	120
gaacaatgcg	aaagcgtttt	cttccctagg	ctgcagattg	tctttcttcac	cgcccttgct	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgatacct	cctagatgca	240

ctcggttttga	gttacaaact	ccgcggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaaat	tatttttagta	tcagaagaat	atcagggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaatg	ttagtttgct	ttccgccatt	tctacagaaa	gctgcaattt	420
cagggttttca	ncctaatagg	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gctttttacaa	atcatttttc	tcttctaggt	atagcctgtc	agggtggccta	atgtattttt	540
gacatctcta	ggaattttta	tagaccagaa	atgggtgcca	gagatatgcc	tgactaatc	600
ttaagtgggg	atttatgtat	ttctcaanca	agtgattaaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct	taaaatngaa	aaaaaaattg	tttaaaccce	naaggtctga	ataccceagc	780
nccctgaacn	anagaacaan	gccggagcac	cccctcccaa	atcccc		826

&lt;210&gt; 603

&lt;211&gt; 817

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(817)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 603

nnangacttt	tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa	taattctaaa	actcatcatg	actttcttgc	ctaaaagatc	ttgatttcaa	120
tcgtgcctag	ttttgcttta	atcacttgct	tgagaaatac	ataaatcccc	acttaagatt	180
agtgcaggca	tatctctggc	acccatttct	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaagca	300
gtggggctat	ttgcgattgc	tttttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca	gctttctgta	gaaatggcgg	aagacaaact	aacattttta	aagcgctctc	420
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&lt;210&gt; 604

&lt;211&gt; 694

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(694)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 604

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<213> Artificial Sequence

<220>  
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<400> 607  
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38

&lt;210&gt; 614

&lt;211&gt; 53

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

&lt;400&gt; 614

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53

&lt;210&gt; 615

&lt;211&gt; 46

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Primer

&lt;400&gt; 615

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46

&lt;210&gt; 616

&lt;211&gt; 1350

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 616

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&lt;210&gt; 617



&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 617

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Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His
 35           40           45
Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu
 50           55           60
Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val
 65           70           75           80
Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu
           85           90           95
Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile
           100          105          110
Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser
           115          120          125
Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys
           130          135          140
Val Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp
           145          150          155          160
Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln
           165          170          175
Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly
           180          185          190
Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val
           195          200          205
Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys Phe Thr Glu Trp Ile
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Glu Lys Thr Val Gln Ala Ser Ile Val Gly Gly Trp Glu Cys Glu Lys
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His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val
           245          250          255
Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His
           260          265          270
Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe
           275          280          285
His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro
           290          295          300
His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro
           305          310          315          320
Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro
           325          330          335
Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln Glu
           340          345          350
Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu
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Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu His
           370          375          380
Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val Thr
           385          390          395          400
Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Trp Gly
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 <211> 3923  
 <212> DNA  
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&lt;211&gt; 3674

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 619

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&lt;210&gt; 620

&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2051)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 620

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aaaaaaaaaa	a					2051

&lt;210&gt; 621

&lt;211&gt; 2841

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2841)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 621

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&lt;210&gt; 622

&lt;211&gt; 3228

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(3228)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 622

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&lt;210&gt; 623

&lt;211&gt; 4894

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 623

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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

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Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys  
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Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly  
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Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu  
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Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly  
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239

Trp Glu Gly Trp Ser Gly Phe Leu Gly Gly Gln Leu Ala Gln Asn Leu  
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Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
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Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro  
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Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr  
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Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly  
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Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly  
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Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala  
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240

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 631

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&lt;211&gt; 684

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      20                      25                      30

Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
      35                      40                      45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
      50                      55                      60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
      65                      70                      75                      80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
      85                      90                      95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
      100                      105                      110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
      115                      120                      125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
      130                      135                      140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
      145                      150                      155                      160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
      165                      170                      175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
      180                      185                      190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
      195                      200                      205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
      210                      215                      220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

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244

225                      230                      235                      240  
 Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr  
~~245~~ ~~250~~ ~~255~~  
 Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala  
                     260                      265                      270  
 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
                     275                      280                      285  
 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
                     290                      295                      300  
 Asp Thr Tyr Val Asn Glu Asn Gly Lys Lys Ile Thr Ser Met Thr His  
                     305                      310                      315                      320  
 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
                     325                      330                      335  
 Pro Asp Leu Pro Lys Gly Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr  
                     340                      345                      350  
 Pro Gln Glu Arg Ser Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu  
                     355                      360                      365  
 Thr Ala Ile Arg Lys Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe  
                     370                      375                      380  
 Val Phe Ser Glu Val Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met  
                     385                      390                      395                      400  
 Val Asn Gly Gln Glu Glu Leu His Val Ile Ser Met Glu Thr Thr Ser  
                     405                      410                      415  
 Ile Gly Lys Asn Ile Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg  
                     420                      425                      430  
 Asp Ile Thr Tyr Glu Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg  
                     435                      440                      445  
 Gln Val Met Asp His Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His  
                     450                      455                      460  
 Arg Arg Pro Val Lys Glu Asn Phe Leu His Met Ser Val Gln Ser Asp  
                     465                      470                      475                      480  
 Asp Val Leu Leu Gly Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg  
                     485                      490                      495  
 Lys Thr Ala Ala Leu Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu  
                     500                      505                      510  
 Gln Leu Tyr Thr Gly Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys  
                     515                      520                      525  
 Thr Ser Gln Ile Gln Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp  
                     530                      535                      540

245

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val  
 545 550 555 560  
 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met  
 565 570 575

Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu  
 580 585 590

Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile  
 595 600 605

Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu  
 610 615 620

Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val  
 625 630 635 640

Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys  
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Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys  
 660 665 670

Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys  
 675 680

<210> 633  
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 <212> PRT  
 <213> Homo sapiens

<400> 633  
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Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser  
 20 25 30

Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu  
 35 40 45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr  
 50 55 60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro  
 65 70 75 80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu  
 85 90 95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile  
 100 105 110

Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys  
 115 120 125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu  
130 135 140

~~Asp Met Val Phe Met Pro Asn Glu Asn Glu Arg Lys Glu Tyr Ile Leu~~  
~~145 150 155 160~~

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys  
165 170 175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys  
180 185 190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp  
195 200 205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys  
210 215 220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly  
225 230 235 240

Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr  
245 250 255

Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala  
260 265 270

Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
275 280 285

Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
290 295 300

Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His  
305 310 315 320

Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
325 330 335

Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser  
340 345 350

Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys  
355 360 365

Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val  
370 375 380

Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu  
385 390 395 400

Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile  
405 410 415

Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu  
420 425 430

Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

435                      440                      445  
 Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys  
     450                      455                      460  
 Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly  
     465                      470                      475                      480  
 Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu  
                     485                      490                      495  
 Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly  
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 Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln  
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 Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile  
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 Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile  
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 Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe  
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 Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly  
                     580                      585                      590  
 Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu  
                     595                      600                      605  
 Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile  
                     610                      615                      620  
 Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr  
     625                      630                      635                      640  
 Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys  
                     645                      650                      655  
 Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys Glu Ile Asn Ala Gln  
                     660                      665                      670  
 Lys Ile Val Leu Ile Thr Lys  
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&lt;210&gt; 634

&lt;211&gt; 5668

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 634

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa

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&lt;210&gt; 635

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 635

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
          5                      10                      15

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Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                      25                      30

```

```

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                      40                      45

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Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                      55                      60

```

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Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
          65                      70                      75                      80

```

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Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
          85                      90                      95

```



250

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Ser Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val  
 370 375 380  
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser  
 385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn  
 405 410 415  
 Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
 435 440 445  
 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
 500 505 510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625 630 635 640  
 Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp  
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 Gln His Phe Thr Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala

252

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		725		730		735
Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His						
		740		745		750
Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val						
		755		760		765
Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr						
		770		775		780
Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe						
		785		790		795
						800
Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu						
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Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu						
		820		825		830
Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile						
		835		840		845
Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu						
		850		855		860
Phe Ala Val Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu						
		865		870		875
						880
Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr						
		885		890		895
Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly						
		900		905		910
Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys						
		915		920		925
Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu						
		930		935		940
Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile						
		945		950		955
						960
Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr						
		965		970		975
Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu						
		980		985		990
Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val						
		995		1000		1005
Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys						
		1010		1015		1020

Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp  
 1025 1030 1035 1040  
 Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val  
 1045 1050 1055  
 Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg  
 1060 1065 1070  
 Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys  
 1075 1080 1085  
 Glu Ile Ala Asn Lys Ile Lys  
 1090 1095

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 <211> 3639  
 <212> DNA  
 <213> Homo sapiens

<400> 636  
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 agcatgagga acagaaggaa tgacactctg gacagcacc ggaccctgta ctccagcgcg 180  
 tctcgagca cagacttgct ttacagtga agcgacttgg tgaattttat tcaagcaaat 240  
 ttttaagaaac gagaatgtgt cttctttacc aaagattcca aggccacgga gaatgtgtgc 300  
 aagtgtggct atgcccagag ccagcacatg gaaggcacc agatcaacca aagtgagaaa 360  
 tggaactaca agaaacacac caaggaattt cctaccgacg cctttgggga tattcagttt 420  
 gagacactgg ggaagaaagg gaagtatata cgtctgtcct gcgacacgga cgcggaatc 480  
 ctttacgagc tgctgaccca gcactggcac ctgaaaacac ccaacctggt catttctgtg 540  
 accgggggag ccaagaactt cgccctgaag ccgcgcacgc gcaagatctt cagccggctc 600  
 atctacatcg cgagtcctaa aggtgcttgg attctcacgg gaggcacca ttatggcctg 660  
 atgaagtaca tcggggagggt ggtgagagat aacaccatca gcaggagttc agaggagaat 720  
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 aatgctgctg gggagtccga ggagctggct aatgagtacg agaccggggc tgttgagctg 1980  
 ttcactgagt gttacagcag cgatgaagac ttggcagaac agctgctggt ctattcctgt 2040

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gaagcttggg gtggaagcaa ctgtctggag ctggcgggtg aggccacaga ccagcatttc 2100
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taaatacccc tagtgtgtg agaccttgag aataaagtgt gaagggcgaa ttctgcagat 3600
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&lt;210&gt; 637

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(1095)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 637

```

Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
          5                      10                      15

```

```

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                      25                      30

```

```

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                      40                      45

```

```

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                      55                      60

```

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
          65                      70                      75                      80

```

```

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
          85                      90                      95

```

```

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

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255

100					105					110					
Cys	Asp	Thr	Asp	Ala	Glu	Ile	Leu	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp
	115						120					125			
His	Leu	Lys	Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys
	130						135					140			
Asn	Phe	Ala	Leu	Lys	Pro	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile
	145						150					155			160
Tyr	Ile	Ala	Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His
				165					170					175	
Tyr	Gly	Leu	Met	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile
			180					185					190		
Ser	Arg	Ser	Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp
		195					200					205			
Gly	Met	Val	Ser	Asn	Arg	Asp	Thr	Leu	Ile	Arg	Asn	Cys	Asp	Ala	Glu
	210						215					220			
Gly	Tyr	Phe	Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro
	225					230					235				240
Leu	Tyr	Ile	Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn
				245					250					255	
Gly	Cys	His	Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu
			260					265					270		
Glu	Lys	Tyr	Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly
		275					280					285			
Lys	Ile	Pro	Ile	Val	Cys	Phe	Ala	Gln	Gly	Gly	Gly	Lys	Glu	Thr	Leu
	290						295					300			
Lys	Ala	Ile	Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val
	305					310					315				320
Glu	Gly	Ser	Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val
			325						330					335	
Glu	Asp	Ala	Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe
			340					345					350		
Leu	Pro	Arg	Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp
		355					360					365			
Ile	Lys	Trp	Leu	Lys	Glu	Ile	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val
	370						375				380				
Ile	Lys	Met	Glu	Glu	Ala	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser
	385					390					395				400
Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn
				405					410					415	

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
 435 440 445  
 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
 500 505 510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625 630 635 640  
 Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp  
 645 650 655  
 Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala  
 705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr  
 725 730 735  
 Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His  
 740 745 750  
 Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val  
 755 760 765  
 Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr  
 770 775 780  
 Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe  
 785 790 795 800  
 Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu  
 805 810 815  
 Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu  
 820 825 830  
 Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile  
 835 840 845  
 Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu  
 850 855 860  
 Phe Ala Xaa Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu  
 865 870 875 880  
 Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr  
 885 890 895  
 Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly  
 900 905 910  
 Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys  
 915 920 925  
 Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu  
 930 935 940  
 Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile  
 945 950 955 960  
 Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr  
 965 970 975  
 Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu  
 980 985 990  
 Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val  
 995 1000 1005  
 Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys  
 1010 1015 1020  
 Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp



258

1025	1030	1035	1040
Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val			
1045	1050	1055	
Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg			
1060	1065	1070	
Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys			
1075	1080	1085	
Glu Ile Ala Asn Lys Ile Lys			
1090	1095		

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 <212> PRT  
 <213> Homo sapiens

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<400> 641  
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<210> 642  
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<400> 642  
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<210> 643  
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<212> DNA  
<213> Homo sapiens

<400> 643  
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<210> 644  
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<210> 657  
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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 657

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				5					10					15

&lt;210&gt; 658

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 658

Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met
				5					10					15

&lt;210&gt; 659

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 659

Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu
				5					10					15

&lt;210&gt; 660

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu
				5					10				

&lt;210&gt; 661

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 661

Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
				5					10					15

&lt;210&gt; 662

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 662

His	Pro	Gln	Trp	Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser
				5					10					15

262

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<210> 664  
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5 10 15

<210> 665  
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<212> PRT  
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<400> 665  
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<210> 666  
<211> 17  
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<400> 666  
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Ser

<210> 667  
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<212> PRT  
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<400> 667  
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5 10 15

<210> 668  
<211> 15  
<212> PRT  
<213> Homo sapiens

263

&lt;400&gt; 668

Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser  
5 10 15

&lt;210&gt; 669

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 669

Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser  
5 10 15

&lt;210&gt; 670

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 670

Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser  
5 10 15

&lt;210&gt; 671

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu  
5 10 15

&lt;210&gt; 672

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 672

ggaccagcat atgaggaaca gaaggaatga cactc

35

&lt;210&gt; 673

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 673

ccgctcgagt ccacccaag cttcacagg

29

```
<210> 675
<211> 652
<212> PRT
<213> Homo sapiens
```

```

<400> 675
Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
          5                      10                      15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
          20                      25                      30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
          35                      40                      45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
          50                      55                      60

```

265

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp  
 65 70 75 80  
 Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp  
 85 90 95  
 Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val



370                      375                      380  
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser  
 385                      390                      395                      400  
 Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn  
                     405                      410                      415  
 Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
                     420                      425                      430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
                     435                      440                      445  
 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
                     450                      455                      460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465                      470                      475                      480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
                     485                      490                      495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
                     500                      505                      510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
                     515                      520                      525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
                     530                      535                      540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545                      550                      555                      560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
                     565                      570                      575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
                     580                      585                      590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
                     595                      600                      605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
                     610                      615                      620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625                      630                      635                      640  
 Ala Trp Gly Gly Leu Glu His His His His His His  
                     645                      650

<210> 676  
 <211> 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 676

```

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1      5      10      15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
      20      25      30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
      35      40      45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
      50      55      60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
      65      70      75      80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
      85      90      95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
      100     105     110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
      115     120     125
Gly Pro Pro Ala
      130

```

&lt;210&gt; 677

&lt;211&gt; 36

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 677

ggggaattca tgatccggga gaaatttgcc cactgc

36

&lt;210&gt; 678

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 678

gggctcgagt caggagtttg agaccagcct ggc

33

&lt;210&gt; 679

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 679

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

```

```

accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgcacgag tccaacgcgt ggtcgggagc gtcctggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cgggtgacgtc atctcgggtga cctggcaaac caagtcgggc 360
ggcgacgcgtg cagggaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgacaaga taatggtttt agattcagga agactgaaag aatatgatga gccgtatggt 540
ttgctgcaaa ataaagagag cctattttac aagatggtgc aacaactggg caaggcagaa 600
gccgctgccc tcaactgaaac agcaaaacag agatgggggt tcacatggt ggccaggctg 660
gtctcaaaact cctga 675

```

&lt;210&gt; 680

&lt;211&gt; 291

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 680

```

atggggatcc gggagaaatt tgccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatggtt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgctgca aaataaagag agcctatttt acaagatggt gcaacaactg 180
ggcaaggcag aagcgcgtgc cctcactgaa acagcaaaac agagatgggg ttccaccatg 240
ttggccaggc tgggtctcaaa ctccctcgag caccaccacc accaccactg a 291

```

&lt;210&gt; 681

&lt;211&gt; 1074

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 681

```

atgtcagcca ttgagagggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgctacttg atgagatadc acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgcttttttg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcac cactgttaag tgccgtgctc ggggaattgg cccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct ggggtgttctc ggggaactctg 360
aggagtaata ttttatttgg gaagaaatac gaaaaggaaac gatatgaaaa agtcataaag 420
gcttgtgctc tgaaaaagga ttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgtgag ttggaggcag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagtaga tgcggaagtt 600
agcagactgc tgttcgaact gtgtatttgc caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaaagct gcaagtcaga ttctgatatt gaaagatggt 720
aaaatgggtgc agaaggggac ttacactgag ttcttaaaat ctggtataga ttttggctcc 780
cttttaaga aggataatga ggaaagtga caacctccag ttccaggaaac tcccacacta 840
aggaatcgta ccttctcaga gtcttcggtt tgggtctcaac aatcttctag accctccttg 900
aaagatgggt ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tggttttcag gcctataaga attacttcag agctgggtgct 1020
cactggattg tcttcatttt ctttattctc gagcaccacc accaccacca ctga 1074

```

&lt;210&gt; 682

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 682

```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
          5                      10                      15

```

```

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```

```
<210> 683
<211> 357
<212> PRT
<213> Homo sapiens
```

<400> 683  
Met Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg Arg  
5 10 15  
Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg Gln  
20 25 30  
Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr Ala  
35 40 45  
Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser Phe

270

50	55	60
Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala		
65	70	75 80
Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser		
	85	90 95
His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln		
	100	105 110
Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys		
	115	120 125
Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu		
	130	135 140
Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly		
	145	150 155 160
Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu		
	165	170 175
Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro		
	180	185 190
Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys		
	195	200 205
Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His Gln		
	210	215 220
Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp Gly		
	225	230 235 240
Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly Ile		
	245	250 255
Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro		
	260	265 270
Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser		
	275	280 285
Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala		
	290	295 300
Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu Glu		
	305	310 315 320
Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe		
	325	330 335
Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Glu His		
	340	345 350
His His His His His		
	355	

271

&lt;210&gt; 684

&lt;211&gt; 96

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 684

Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala  
5 10 15

His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp  
20 25 30

Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn  
35 40 45

Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu  
50 55 60

Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met  
65 70 75 80

Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His  
85 90 95

&lt;210&gt; 685

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 685

cgcccatggg gatccgggag aaatttgccc actgc

35

&lt;210&gt; 686

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 686

cgctcggagg gagtttgaga ccagcctggc caaca

35

&lt;210&gt; 687

&lt;211&gt; 38

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

<400> 687  
gcatggacca tatgtcagcc attgagaggg tgtcagag 38

<210> 688  
<211> 34  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 688  
ccgctcgaga ataaggaâaa tgaagacaat ccag 34

<210> 689  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 689  
gttgaattca tgcacggggcc ccaggtg 27

<210> 690  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 690  
cccctcgagt cactatggtc tgcctcttga 30

<210> 691  
<211> 915  
<212> DNA  
<213> Homo sapiens

<400> 691  
atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60  
cagggtattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120  
accgttcata tgggcctac cgccttctct ggcttgggtg ttgtcgacaa caacggcaac 180  
ggcgacagag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240  
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300  
gcgtttaacg ggcacatcc cggtagacgt atctcgggtga cctggcaaac caagtggggc 360  
ggcacgcgta cagggaaact gacattggcc gagggacccc cggccgaatt catgcacggg 420  
ccccagggtgc tggcacgctg ctccgagtggt gcttgtcctg ccttgggtgc cacctctgcg 480  
ggggtgcgtc tggagggggg ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540  
ccatgttccc acagcctgag tggctgccac ctgatggctg atggagcaaa ggccttagga 600  
aaagcagatg gcccttggcc ctaccttttt gttagaagaa ctgatgttcc atgtcctgca 660  
gcgagtgagg ttggtggctg tgcccccagc tcctggcgcg ccctcgcaga ggtgactggt 720

```
<210> 692
<211> 304
<212> PRT
<213> Homo sapiens
```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu  
5 10 15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala  
20 25 30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala  
35 40 45

Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val  
50 55 60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr  
65 70 75 80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr  
85 90 95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser  
100 105 110

Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr  
115 120 125

: Leu Ala Glu Gly Pro Pro Ala Glu Phe Met His Gly Pro Gln Val Leu  
130 135 140

Ala Arg Cys Ser Glu Cys Ala Cys Pro Ala Leu Ala Ala Thr Ser Ala  
145 150 155 160

Gly Val Arg Leu Glu Gly Val Asp Arg Pro Pro Thr Leu Pro Ser Gln  
165 170 175

Gly Ser Gly Trp Pro Cys Ser His Ser Leu Ser Gly Cys His Leu Met  
180 185 190

Ala Asp Gly Ala Lys Ala Leu Gly Lys Ala Asp Gly Pro Trp Pro Tyr  
195 200 205

Leu Phe Val Arg Arg Thr Asp Val Pro Cys Pro Ala Ala Ser Glu Val  
210 215 220

Gly Gly Cys Ala Pro Ser Ser Trp Arg Ala Leu Ala Glu Val Thr Gly  
225 230 235 240

Cys Ser Leu Gly Pro Leu Gly Leu Ala Gln His Ala Gln Ala Ser Val-  
245 . 250 . 255



274

Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His  
 260 265 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu  
 275 280 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro  
 290 295 300

&lt;210&gt; 693

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 693

cgaagtcacg tggaggccag cctc

24

&lt;210&gt; 694

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 694

cctgaccgaa ttcattaact ggcctggac

29

&lt;210&gt; 695

&lt;211&gt; 166

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(166)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 695

Met Gly His His His His His Val Glu Ala Ser Leu Ser Val Arg  
 1 5 10 15  
 His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile  
 20 25 30  
 Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser  
 35 40 45  
 Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly  
 50 55 60  
 Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val  
 65 70 75 80  
 Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro

[illegible]

<400>	696							
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aacagaccct	tgctcgctaa	cgacctcatg	ctcatcaagt	tggacgaatc	cgtgtccgag			120
tctgacacca	tccggagcat	cagcattgct	tcgcaagtgcc	ctaccgcggg	gaactcttgc			180
ctcgtttctg	gctggggctc	gctggcgaa	ggcagaatgc	ctaccgtgct	gcagtgcgtg			240
aacgtgtcgg	tggtgtctga	ggaggtctgc	agtaagctct	atgaccgcgt	gtaccacccc			300
agcatgctct	gcgcggccgg	aggggcaanac	cagaangact	ccttgcacgg	tgactctggg			360
gggcccttga	tctgcaacgg	gtacttgcag	ggccttgtgt	ctttcgaaa	agccccgtgt			420
ggccaagtgt	gcgtgcacgg	tgtctacacc	aacctctgca	aattcactga	gtggatagag			480
aaaaccgtcc	aggccagtta	atga						504

<400> 697  
ctcagggttc cggagccgcg g 21

<400> 698  
ctatagaatt cattaccaa aagctgggct ccagc 35

<210> 699

<211> 241  
 <212> PRT  
 <213> Homo sapiens

<400> 699

```

Met Gln His His His His His His Leu Arg Val Pro Glu Pro Arg Pro
 1           5           10           15
Gly Glu Ala Lys Ala Glu Gly Ala Ala Pro Pro Thr Pro Ser Lys Pro
      20           25           30
Leu Thr Ser Phe Leu Ile Gln Asp Ile Leu Arg Asp Gly Ala Gln Arg
      35           40           45
Gln Gly Gly Arg Thr Ser Ser Gln Arg Gln Arg Asp Pro Glu Pro Glu
      50           55           60
Pro Glu Pro Glu Pro Glu Gly Gly Arg Ser Arg Ala Gly Ala Gln Asn
      65           70           75           80
Asp Gln Leu Ser Thr Gly Pro Arg Ala Ala Pro Glu Glu Ala Glu Thr
      85           90           95
Leu Ala Glu Thr Glu Pro Glu Arg His Leu Gly Ser Tyr Leu Leu Asp
      100          105          110
Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr Pro Lys
      115          120          125
Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln Val Ile
      130          135          140
Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala Pro Glu
      145          150          155          160
Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln Val Lys
      165          170          175
Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln Leu Ser
      180          185          190
Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala Leu Lys
      195          200          205
Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn Ser Tyr
      210          215          220
Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro Ala Phe
      225          230          235          240
Trp

```

<210> 700  
 <211> 729  
 <212> DNA  
 <213> Homo sapiens

<400> 700

```

atgcagcatc accaccatca ccacctcagg gttccggagc cgcggcccgg ggaggcgaaa      60
gcggaggggg ccgcgccgcc gaccccgctc aagccgctca cgtccttcct catccaggac      120
atcctgcggg acggcgcgca gcggcaaggc ggccgcacga gcagccagag acagcgcgac      180
ccggagccgg agccagagcc agagccagag ggaggacgca gccgcgccgg ggcgcgagac      240
gaccagctga gcaccggggc ccgcgcgcgg ccggatgagg ccgagacgct ggcagagacc      300
gagccagaaa ggcacttggg gtcttatctg ttggactctg aaaacacttc aggcgccttc      360
ccaaggcttc cccaaacccc taagcagccg cagaagcgct cccgagctgc cttctccac      420
actcaggtga tcgagttgga gaggaagttc agccatcaga agtacctgtc ggcccctgaa      480
cgggcccacc tggccaagaa cctcaagctc acggagaccc aagtgaagat atggttccag      540
aacagacgct ataagactaa gcgaaagcag ctctcctcgg agctgggaga cttggagaag      600
cactcctttt tgccggccct gaaagaggag gccttctccc ggcctccct ggtctccgtg      660
tataacagct atccttacta cccatacctg cactgcgtgg gcagctggag cccagctttt      720
tggtaatga

```

277

<210> 701  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 701  
 ctactaagcg ctggagtgag ggatcag

27

<210> 702  
 <211> 33  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 702  
 catcgagaat tcactactct ctgactagat gtc

33

<210> 703  
 <211> 161  
 <212> PRT  
 <213> Homo sapiens

<400> 703  
 Met Gln His His His His His Ala Gly Val Arg Asp Gln Gly Gln  
 1 5 10 15  
 Gly Ala Arg Trp Pro His Thr Gly Lys Arg Gly Pro Leu Leu Gln Gly  
 20 25 30  
 Leu Thr Trp Ala Thr Gly Gly His Cys Phe Ser Ser Glu Glu Ser Gly  
 35 40 45  
 Ala Val Asp Gly Ala Gly Gln Lys Lys Asp Arg Ala Trp Leu Arg Cys  
 50 55 60  
 Pro Glu Ala Val Ala Gly Phe Pro Leu Gly Ser Asp Cys Arg Glu Gly  
 65 70 75 80  
 Gly Arg Gln Gly Cys Gly Gly Ser Asp Asp Glu Asp Asp Leu Gly Val  
 85 90 95  
 Ala Pro Gly Leu Ala Pro Ala Trp Ala Leu Thr Gln Pro Pro Ser Gln  
 100 105 110  
 Ser Pro Gly Pro Gln Ser Leu Pro Ser Thr Pro Ser Ser Ile Trp Pro  
 115 120 125  
 Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His  
 130 135 140  
 Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg  
 145 150 155 160  
 Glu

<210> 704  
 <211> 489  
 <212> DNA  
 <213> Homo sapiens

<400>	704						
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cctcacacag	ggaagagagg	gcccctcctg	cagggcctca	cctgggccac	aggaggacac		120
tgcttttcct	ctgaggagtc	aggagctgtg	gatggtgctg	gacagaagaa	ggacagggcc		180
tggtcaggt	gtccagaggc	tgtcgctggc	ttccctttgg	gatcagaactg	cagggagggga		240
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gcccctgcct	gggcctcac	ccagcctccc	tcacagtctc	ctggccctca	gtctctcccc		360
tcactccat	ctccatctg	gcctcagtg	gtcattctga	tactgaact	gaccataccc		420
agccctgcc	acggccctcc	atggctcccc	aatgccctgg	agaggggaca	tctagtca		480
gagtagtga							489

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<210> 705  
<211> 132  
<212> PRT  
<213> Homo sapiens
```

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<400> 705
Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
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Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
          20          25          30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
          35          40          45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
          50          55          60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65          70          75          80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
          85          90          95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
          100          105          110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
          115          120          125
Gly Pro Pro Ala
130

```

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<210> 706
<211> 31
<212> DNA
<213> Artificial Sequence
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<220>  
<223> PCR primer

<400> 706  
ggggaattca tcacctatgt gccgcctctg c

31

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<210> 707
<211> 40
<212> DNA
<213> Artificial Sequence
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<220>  
<223> PCR primer

&lt;400&gt; 707

gggctcgagt cactcgccca cgaaatccgt gtaaaacagc

40

&lt;210&gt; 708

&lt;211&gt; 1203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 708

```

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cccctggagc tggcactgct catcctgggc gtggggctgc tggacttctg tggccagggtg 720
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tga 1203

```

&lt;210&gt; 709

&lt;211&gt; 400

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 709

```

Met His His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
      5              10              15

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala
      20              25              30

Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala
      35              40              45

Phe Leu Gly Leu Gly Val Val Asn Asn Gly Asn Gly Ala Arg Val
      50              55              60

Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr
      65              70              75              80

Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr
      85              90              95

Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser

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280

100					105					110					
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr
		115					120					125			
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Ile	Thr	Tyr	Val	Pro	Pro	Leu
	130					135					140				
Leu	Leu	Glu	Val	Gly	Val	Glu	Glu	Lys	Phe	Met	Thr	Met	Val	Leu	Gly
145					150					155					160
Ile	Gly	Pro	Val	Leu	Gly	Leu	Val	Cys	Val	Pro	Leu	Leu	Gly	Ser	Ala
				165				170						175	
Ser	Asp	His	Trp	Arg	Gly	Arg	Tyr	Gly	Arg	Arg	Arg	Pro	Phe	Ile	Trp
			180					185					190		
Ala	Leu	Ser	Leu	Gly	Ile	Leu	Leu	Ser	Leu	Phe	Leu	Ile	Pro	Arg	Ala
		195					200						205		
Gly	Trp	Leu	Ala	Gly	Leu	Leu	Cys	Pro	Asp	Pro	Arg	Pro	Leu	Glu	Leu
	210					215					220				
Ala	Leu	Leu	Ile	Leu	Gly	Val	Gly	Leu	Leu	Asp	Phe	Cys	Gly	Gln	Val
225					230					235					240
Cys	Phe	Thr	Pro	Leu	Glu	Ala	Leu	Leu	Ser	Asp	Leu	Phe	Arg	Asp	Pro
				245					250					255	
Asp	His	Cys	Arg	Gln	Ala	Tyr	Ser	Val	Tyr	Ala	Phe	Met	Ile	Ser	Leu
			260					265					270		
Gly	Gly	Cys	Leu	Gly	Tyr	Leu	Leu	Pro	Ala	Ile	Asp	Trp	Asp	Thr	Ser
		275					280					285			
Ala	Leu	Ala	Pro	Tyr	Leu	Gly	Thr	Gln	Glu	Glu	Cys	Leu	Phe	Gly	Leu
	290					295					300				
Leu	Thr	Leu	Ile	Phe	Leu	Thr	Cys	Val	Ala	Ala	Thr	Leu	Leu	Val	Ala
305					310					315					320
Glu	Glu	Ala	Ala	Leu	Gly	Pro	Thr	Glu	Pro	Ala	Glu	Gly	Leu	Ser	Ala
				325					330					335	
Pro	Ser	Leu	Ser	Pro	His	Cys	Cys	Pro	Cys	Arg	Ala	Arg	Leu	Ala	Phe
			340					345					350		
Arg	Asn	Leu	Gly	Ala	Leu	Leu	Pro	Arg	Leu	His	Gln	Leu	Cys	Cys	Arg
		355					360					365			
Met	Pro	Arg	Thr	Leu	Arg	Arg	Leu	Phe	Val	Ala	Glu	Leu	Cys	Ser	Trp
	370					375					380				
Met	Ala	Leu	Met	Thr	Phe	Thr	Leu	Phe	Tyr	Thr	Asp	Phe	Val	Gly	Glu
385					390					395					400

281

<210> 710  
<211> 20  
<212> PRT  
<213> Homo sapiens

<400> 710  
Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val  
5 10 15

Ser Val Arg Val  
20

<210> 711  
<211> 60  
<212> DNA  
<213> Homo sapiens

<400> 711  
ctgctccac ctccaccgc gctctgcggg gcctctgcct gtgatgtctc cgtacgtgtg 60

<210> 712  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 712  
Ala Ser Ala Cys Asp Val Ser Val Arg Val  
5 10

<210> 713  
<211> 30  
<212> DNA  
<213> Homo sapiens

<400> 713  
gcctctgcct gtgatgtctc cgtacgtgtg 30

<210> 714  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 714  
Ala Ser Ala Cys Asp Val Ser Val Arg  
1 5

<210> 715  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 715  
Ser Ala Cys Asp Val Ser Val Arg Val  
5

<210> 716  
<211> 27



282

<212> DNA  
<213> Homo sapiens

<400> 716  
tctgcctgtg atgtctccgt acgtgtg

27

<210> 717  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 717  
Gly Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser  
5 10 15

Ala Ser Asp

<210> 718  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 718  
Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr  
5 10 15

Met Val Leu

<210> 719  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 719  
Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala  
5 10 15

Gln Leu Leu

<210> 720  
<211> 57  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(57)  
<223> n = A,T,C or G

<400> 720  
ggnathggnc cngtnytngg nytngtntgy gtncnytny tnggnwsngc nwsngay 57

<210> 721  
<211> 57  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
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<223> n = A,T,C or G

<400> 721  
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<210> 722  
<211> 57  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(57)  
<223> n = A,T,C or G

<400> 722  
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<210> 723  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 723  
Val Leu Gln Cys Val Asn Val Ser Val  
1 5

<210> 724  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 724  
Arg Met Pro Thr Val Leu Gln Cys Val  
1 5

<210> 725  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 725  
Asn Leu Cys Lys Phe Thr Glu Trp Ile  
1 5

<210> 726  
<211> 9  
<212> PRT

<213> Homo sapiens

<400> 726

Met Leu Ile Lys Leu Asp Glu Ser Val  
1 5

<210> 727

<211> 9

<212> PRT

<213> Homo sapiens

<400> 727

Leu Leu Ala Asn Asp Leu Met Leu Ile  
1 5

<210> 728

<211> 10

<212> PRT

<213> Homo sapiens

<400> 728

Leu Leu Ala Asn Gly Arg Met Pro Thr Val  
1 5 10

<210> 729

<211> 10

<212> PRT

<213> Homo sapiens

<400> 729

Leu Met Leu Ile Lys Leu Asp Glu Ser Val  
1 5 10

<210> 730

<211> 10

<212> PRT

<213> Homo sapiens

<400> 730

Val Leu Gln Cys Val Asn Val Ser Val Val  
1 5 10

<210> 731

<211> 10

<212> PRT

<213> Homo sapiens

<400> 731

Gly Leu Leu Ala Asn Gly Arg Met Pro Thr  
1 5 10

<210> 732

<211> 10

<212> PRT

<213> Homo sapiens

<400> 732

Thr Val Leu Gln Cys Val Asn Val Ser Val

285

1 5 10

&lt;210&gt; 733

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 733

Gly Val Leu Val His Pro Gln Trp Val

1 5

&lt;210&gt; 734

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 734

Val Leu Val His Pro Gln Trp Val Leu

1 5

&lt;210&gt; 735

&lt;211&gt; 1195

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 735

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ggagaaaattt agaagaagac gattatttgc ataaggacac gggagagacc agcatgctaa 180
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&lt;210&gt; 736

&lt;211&gt; 339

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 736

Met Glu Ser Arg Lys Asp Ile Thr Asn Gln Glu Glu Leu Trp Lys Met

5

10

15

Lys Pro Arg Arg Asn Leu Glu Glu Asp Asp Tyr Leu His Lys Asp Thr  
                     20                    25                    30  
 Gly Glu Thr Ser Met Leu Lys Arg Pro Val Leu Leu His Leu His Gln  
                     35                    40                    45  
 Thr Ala His Ala Asp Glu Phe Asp Cys Pro Ser Glu Leu Gln His Thr  
                     50                    55                    60  
 Gln Glu Leu Phe Pro Gln Trp His Leu Pro Ile Lys Ile Ala Ala Ile  
                     65                    70                    75                    80  
 Ile Ala Ser Leu Thr Phe Leu Tyr Thr Leu Leu Arg Glu Val Ile His  
                     85                    90                    95  
 Pro Leu Ala Thr Ser His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu  
                     100                    105                    110  
 Val Ile Asn Lys Val Leu Pro Met Val Ser Ile Thr Leu Leu Ala Leu  
                     115                    120                    125  
 Val Tyr Leu Pro Gly Val Ile Ala Ala Ile Val Gln Leu His Asn Gly  
                     130                    135                    140  
 Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr  
                     145                    150                    155                    160  
 Arg Lys Gln Phe Gly Leu Leu Ser Phe Phe Phe Ala Val Leu His Ala  
                     165                    170                    175  
 Ile Tyr Ser Leu Ser Tyr Pro Met Arg Arg Ser Tyr Arg Tyr Lys Leu  
                     180                    185                    190  
 Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp Ala Trp  
                     195                    200                    205  
 Ile Glu His Asp Val Trp Arg Met Glu Ile Tyr Val Ser Leu Gly Ile  
                     210                    215                    220  
 Val Gly Leu Ala Ile Leu Ala Leu Leu Ala Val Thr Ser Ile Pro Ser  
                     225                    230                    235                    240  
 Val Ser Asp Ser Leu Thr Trp Arg Glu Phe His Tyr Ile Gln Ser Lys  
                     245                    250                    255  
 Leu Gly Ile Val Ser Leu Leu Leu Gly Thr Ile His Ala Leu Ile Phe  
                     260                    265                    270  
 Ala Trp Asn Lys Trp Ile Asp Ile Lys Gln Phe Val Trp Tyr Thr Pro  
                     275                    280                    285  
 Pro Thr Phe Met Ile Ala Val Phe Leu Pro Ile Val Val Leu Ile Phe  
                     290                    295                    300  
 Lys Ser Ile Leu Phe Leu Pro Cys Leu Arg Lys Lys Ile Leu Lys Ile  
                     305                    310                    315                    320  
 Arg His Gly Trp Glu Asp Val Thr Lys Ile Asn Lys Thr Glu Ile Cys

325

330

335

Ser Gln Leu

&lt;210&gt; 737

&lt;211&gt; 2172

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 737

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aaaattgaat attgagatac cattcttttag tgttaccttt tttaccacaca tgtgtttctg 60
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gtttggtgat caaacaactg ctggccaaaa atgatgagta tttcccctc ttgctgaaga 2160
tgtgtccat ac 2172
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&lt;210&gt; 738

&lt;211&gt; 2455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 738

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```

&lt;210&gt; 739

&lt;211&gt; 2455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 739

```

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```

```
<210> 740
<211> 62
<212> PRT
<213> Homo sapiens
```

<400> 740  
Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn  
5 10 15  
His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln  
20 25 30  
Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu  
35 40 45  
Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala  
50 55 60

```
<210> 741
<211> 135
<212> PRT
<213> Homo sapiens
```

<400> 741  
Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg  
5 10 15



```
<210> 742
<211> 77
<212> PRT
<213> Homo sapiens
```

```

<400> 742
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
          5                      10                      15
Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
          20                      25                      30
Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
          35                      40                      45
Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
          50                      55                      60
Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
          65                      70                      75

```

```
<210> 743
<211> 60
<212> PRT
<213> Homo sapiens
```

<400> 743  
Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
5 10 15  
Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
20 25 30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
 35 40 45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
 50 55 60

<210> 744  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 744  
 Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
 5 10 15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
 20 25 30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
 35 40 45  
 Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
 50 55 60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
 65 70 75

<210> 745  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 745  
 Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp  
 5 10 15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
 20 25 30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
 35 40 45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
 50 55 60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
 65 70 75

<210> 746  
 <211> 80  
 <212> PRT  
 <213> Homo sapiens

<400> 746  
 Met Leu Leu His Ser Ser Leu Val Asn Arg Ala Arg Leu Cys Leu Lys

				5					10					15	
Asn	Lys	Gln	Ile	Asn	Lys	Gln	Thr	Asn	Lys	Thr	Glu	Arg	Phe	Cys	Cys
				20					25					30	
Asn	Val	Gln	Gly	Ala	Ile	Cys	Ser	Phe	Lys	Lys	Ile	Ile	Phe	Gly	Gln
				35					40					45	
Ala	Gln	Trp	Leu	Thr	Pro	Val	Ile	Pro	Ala	Leu	Trp	Glu	Ala	Lys	Val
				50					55					60	
Gly	Gly	Ser	Phe	Glu	Val	Arg	Ser	Leu	Arg	Ser	Ala	Trp	Pro	Thr	Trp
				65					70					75	80

```
<210> 747
<211> 72
<212> PRT
<213> Homo sapiens
```

```

<400> 747
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro His Asn Pro
          5                      10                      15

Ile Thr Ser His Gln Val Ser Ser Asp Thr Trp Asp Trp Val Gly Thr
          20                      25                      30

Gln Ser Gln Thr Val Ser Asp Ala Ala Gly Ala Gly Asp Thr Glu Thr
          35                      40                      45

Thr Gln Thr Trp Cys Leu Cys His Ser Ser Gly Leu Cys Leu Ser Pro
          50                      55                      60

Gly Pro Pro Ser Pro Ser Met Val
          65                      70

```

```
<210> 748
<211> 77
<212> PRT
<213> Homo sapiens
```

```

<400> 748
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln
      5              10              15
Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His
      20              25              30
Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro
      35              40              45
Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln
      50              55              60
Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu
      65              70              75

```

&lt;210&gt; 749

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 749

Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
                                   5                                  10                                  15

Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
                                   20                                  25                                  30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
                                   35                                  40                                  45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
                                   50                                  55                                  60

&lt;210&gt; 750

&lt;211&gt; 76

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 750

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                                   5                                  10                                  15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                                   20                                  25                                  30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                                   35                                  40                                  45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
                                   50                                  55                                  60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
                                   65                                  70                                  75

&lt;210&gt; 751

&lt;211&gt; 2479

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 751

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 cggaaaaccc ctatcccgca cagcccaactg tggccccac tgtctacgag gtgcatccgg 180  
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 agaaagcact gtgcatcacc ttgaccctgg ggaccttcct cgtgggagct gcgctggccg 360  
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 cctcaggtac ctgcatcaac ccctctaact ggtgtgatgg cgtgtcacac tgccccggcg 480  
 gggaggacga gaatcgggtg ttgcgcctct acggaccaaa cttcacacct cagatgtaet 540  
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```

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2479

```

&lt;210&gt; 752

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 752

```

Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
          5                      10                      15

```

```

Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
          20                      25                      30

```

```

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
          35                      40                      45

```

```

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
          50                      55                      60

```

```

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
          65                      70                      75                      80

```

```

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
          85                      90                      95

```

```

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys

```

100					105					110					
Cys	Ser	Asn	Ser	Gly	Ile	Glu	Cys	Asp	Ser	Ser	Gly	Thr	Cys	Ile	Asn
		115					120					125			
Pro	Ser	Asn	Trp	Cys	Asp	Gly	Val	Ser	His	Cys	Pro	Gly	Gly	Glu	Asp
		130				135					140				
Glu	Asn	Arg	Cys	Val	Arg	Leu	Tyr	Gly	Pro	Asn	Phe	Ile	Leu	Gln	Met
145					150					155					160
Tyr	Ser	Ser	Gln	Arg	Lys	Ser	Trp	His	Pro	Val	Cys	Gln	Asp	Asp	Trp
			165						170					175	
Asn	Glu	Asn	Tyr	Gly	Arg	Ala	Ala	Cys	Arg	Asp	Met	Gly	Tyr	Lys	Asn
			180					185					190		
Asn	Phe	Tyr	Ser	Ser	Gln	Gly	Ile	Val	Asp	Asp	Ser	Gly	Ser	Thr	Ser
		195					200					205			
Phe	Met	Lys	Leu	Asn	Thr	Ser	Ala	Gly	Asn	Val	Asp	Ile	Tyr	Lys	Lys
	210						215				220				
Leu	Tyr	His	Ser	Asp	Ala	Cys	Ser	Ser	Lys	Ala	Val	Val	Ser	Leu	Arg
225					230					235					240
Cys	Leu	Ala	Cys	Gly	Val	Asn	Leu	Asn	Ser	Ser	Arg	Gln	Ser	Arg	Ile
				245					250					255	
Val	Gly	Gly	Glu	Ser	Ala	Leu	Pro	Gly	Ala	Trp	Pro	Trp	Gln	Val	Ser
			260					265					270		
Leu	His	Val	Gln	Asn	Val	His	Val	Cys	Gly	Gly	Ser	Ile	Ile	Thr	Pro
		275					280					285			
Glu	Trp	Ile	Val	Thr	Ala	Ala	His	Cys	Val	Glu	Lys	Pro	Leu	Asn	Asn
	290					295					300				
Pro	Trp	His	Trp	Thr	Ala	Phe	Ala	Gly	Ile	Leu	Arg	Gln	Ser	Phe	Met
305					310					315					320
Phe	Tyr	Gly	Ala	Gly	Tyr	Gln	Val	Gln	Lys	Val	Ile	Ser	His	Pro	Asn
				325					330					335	
Tyr	Asp	Ser	Lys	Thr	Lys	Asn	Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln
			340					345					350		
Lys	Pro	Leu	Thr	Phe	Asn	Asp	Leu	Val	Lys	Pro	Val	Cys	Leu	Pro	Asn
		355					360					365			
Pro	Gly	Met	Met	Leu	Gln	Pro	Glu	Gln	Leu	Cys	Trp	Ile	Ser	Gly	Trp
	370					375					380				
Gly	Ala	Thr	Glu	Glu	Lys	Gly	Lys	Thr	Ser	Glu	Val	Leu	Asn	Ala	Ala
385					390					395					400
Lys	Val	Leu	Leu	Ile	Glu	Thr	Gln	Arg	Cys	Asn	Ser	Arg	Tyr	Val	Tyr
				405					410					415	

Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly  
420 425 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser  
435 440 445

Asn Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly  
450 455 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe  
465 470 475 480

Thr Asp Trp Ile Tyr Arg Gln Met Lys Ala Asn Gly  
485 490

<210> 753

<211> 683

<212> DNA

<213> Homo sapiens

<400> 753

```
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cggaaaaccc ctatcccgca cagcccactg tggccccac tgtctacgag gtgcatccgg 180
ctcagtacta cccgtcccc gtgccccagt acgccccgag ggtcctgacg caggcttcca 240
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```

<210> 754

<211> 209

<212> PRT

<213> Homo sapiens

<400> 754

```
Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
1      5      10      15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20     25     30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35     40     45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50     55     60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65     70     75     80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85     90     95
```

297

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys  
                   100                  105                  110  
 Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn  
                   115                  120                  125  
 Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp  
                   130                  135                  140  
 Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met  
 145                  150                  155                  160  
 Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp  
                   165                  170                  175  
 Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn  
                   180                  185                  190  
 Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser  
                   195                  200                  205  
 Phe

<210> 755  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 755  
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
   1                  5                  10                  15  
 Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg  
                   20                  25

<210> 756  
 <211> 35  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 756  
 ggatccgccg ccaccatgtc actttctagc ctgct

35

<210> 757  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 757  
 gtcgactcag ctggaccaca gccgcag

27

<210> 758  
 <211> 34  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer



<400> 758  
ggatccgccg ccaccatggg ctgcaggctg ctct

34

<210> 759  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 759  
gtcgactcag aaatcctttc tottgac

27

<210> 760  
<211> 936  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 760  
atgggctgca ggctgntctg ctgtgogggt ctctgtctcc tgggagcggg ccccatggaa 60  
acgggagtta cgcagacacc aagacacctg gtcattggga tgacaaataa gaagtctttg 120  
aaatgtgaac aacatctggg tcataacgct atgtattggg acaagcaaag tgctaagaag 180  
ccactggagc tcatgtttgt ctacagtctt gaagaacggg ttgaaaacaa cagtgtgcca 240  
agtgcgttct cacctgaatg ccccaacagc tctcacttat tcttcacct acacaccctg 300  
cagccagaag actcggccct gtatctctgc gccagcagcc aagaccggac aagcagctcc 360  
tacgagcagt acttcgggcc gggcaccagg ctacaggtca cagaggacct gaaaaacgtg 420  
ttcccaccgg aggtcgctgt gtttgagcca tcagaagcag agatctccca caccctaaaag 480  
gccacactgg tgtgcctggc cacaggcttc taccctgacc acgtggagct gagctggtgg 540  
gtgaatggga aggaggtgca cagtgggggc agcacagacc cgcagcccct caaggagcag 600  
cccgcctcca atgactccag atactgcctg agcagccgcc tgaggggtct ggccaccttc 660  
tggcagaacc cccgcaacca cttccgctgt caagtccagt tctacgggct ctcgagaaat 720  
gacgagtggg cccaggatag ggccaaacct gtcacccaga tctgcagcgc cgaggcctgg 780  
ggtagagcag actgtggctt cacctccgag tcttaccagc aaggggtcct gtctgccacc 840  
atcctctatg agatcttgct aggggaaggcc acctgtatg ccgtgctggg cagtgccttc 900  
gtgctgatgg ccattggtcaa gagaaaggat ttctga 936

<210> 761  
<211> 834  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 761  
atgtcacttt ctagcctgct naagggtggc acagcttcac tgtggctagg acctggcatt 60  
gccagaaga taactcaaac ccaaccagga atgttcgtgc aggaaaagga ggctgtgact 120  
ctggactgca catatgacac cagtgatcaa agttatggc tcttctggta caagcagccc 180

```

agcagtgggg aaatgatttt tcttatttat caggggtctt atgacgagca aaatgcaaca 240
gaaggtcgct actcattgaa tttccagaag gcaagaaaat ccgccaacct tgtcatctcc 300
gcttcacaac tgggggactc agcaatgtat ttctgtgcaa tgagagaggg cgcgggagga 360
ggaaacaaac tcacctttgg gacaggcact cagctaaaag tggaactcaa tatccagaac 420
cctgaccctg ccgtgtacca gctgagagac tctaaatcca gtgacaagtc tgtctgccta 480
ttcaccgatt ttgattctca aacaaatgtg tcacaaagta aggattctga tgtgtatata 540
acagacaaaa ctgtgctaga catgaggtct atggacttca agagcaacag tgctgtggcc 600
tggagcaaca aatctgactt tgcattgtgca aacgccttca acaacagcat tattccagaa 660
gacaccttct tcccagccc agaaagttcc tgtgatgtca agctggtcga gaaaagcttt 720
gaaacagata cgaacctaaa ctttcaaac ctgtcagtga ttgggttccg aatcctctc 780
ctgaaagtgg ccgggtttta tctgctcatg acgctgcggc tgtggtccag ctga 834

```

&lt;210&gt; 762

&lt;211&gt; 311

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; variant

&lt;222&gt; (1)...(311)

&lt;223&gt; Xaa = Any amino acid

&lt;400&gt; 762

```

Met Gly Cys Arg Leu Xaa Cys Cys Ala Val Leu Cys Leu Leu Gly Ala
      5                      10                      15

```

```

Val Pro Met Glu Thr Gly Val Thr Gln Thr Pro Arg His Leu Val Met
      20                      25                      30

```

```

Gly Met Thr Asn Lys Lys Ser Leu Lys Cys Glu Gln His Leu Gly His
      35                      40                      45

```

```

Asn Ala Met Tyr Trp Tyr Lys Gln Ser Ala Lys Lys Pro Leu Glu Leu
      50                      55                      60

```

```

Met Phe Val Tyr Ser Leu Glu Glu Arg Val Glu Asn Asn Ser Val Pro
      65                      70                      75                      80

```

```

Ser Arg Phe Ser Pro Glu Cys Pro Asn Ser Ser His Leu Phe Leu His
      85                      90                      95

```

```

Leu His Thr Leu Gln Pro Glu Asp Ser Ala Leu Tyr Leu Cys Ala Ser
      100                      105                      110

```

```

Ser Gln Asp Arg Thr Ser Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly
      115                      120                      125

```

```

Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
      130                      135                      140

```

```

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
      145                      150                      155                      160

```

```

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
      165                      170                      175

```

```

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
      180                      185                      190

```

300

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr  
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro  
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn  
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser  
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr  
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly  
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala  
290 295 300

Met Val Lys Arg Lys Asp Phe  
305 310

<210> 763

<211> 277

<212> PRT

<213> Homo sapiens

<400> 763

Met Ser Leu Ser Ser Leu Leu Lys Val Val Thr Ala Ser Leu Trp Leu  
5 10 15

Gly Pro Gly Ile Ala Gln Lys Ile Thr Gln Thr Gln Pro Gly Met Phe  
20 25 30

Val Gln Glu Lys Glu Ala Val Thr Leu Asp Cys Thr Tyr Asp Thr Ser  
35 40 45

Asp Gln Ser Tyr Gly Leu Phe Trp Tyr Lys Gln Pro Ser Ser Gly Glu  
50 55 60

Met Ile Phe Leu Ile Tyr Gln Gly Ser Tyr Asp Glu Gln Asn Ala Thr  
65 70 75 80

Glu Gly Arg Tyr Ser Leu Asn Phe Gln Lys Ala Arg Lys Ser Ala Asn  
85 90 95

Leu Val Ile Ser Ala Ser Gln Leu Gly Asp Ser Ala Met Tyr Phe Cys  
100 105 110

Ala Met Arg Glu Gly Ala Gly Gly Gly Asn Lys Leu Thr Phe Gly Thr  
115 120 125

Gly Thr Gln Leu Lys Val Glu Leu Asn Ile Gln Asn Pro Asp Pro Ala  
130 135 140

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu  
 145 150 155 160  
 Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser  
 165 170 175  
 Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp  
 180 185 190  
 Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala  
 195 200 205  
 Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe  
 210 215 220  
 Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe  
 225 230 235 240  
 Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe  
 245 250 255  
 Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu  
 260 265 270  
 Arg Leu Trp Ser Ser  
 275

&lt;210&gt; 764

&lt;211&gt; 1536

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 764

atgtacaacc tgttgctgtc ctacgacaga catggggacc acctgcagcc cctggacctc 60  
 gtgcccaatc accaggggtc caccctttc aagctggctg gaggaggagg taacactgtg 120  
 atgtttcagc acctgatgca gaagcggaag cacaccagc ggacgtatgg accactgacc 180  
 tcgactctct atgacctcac agagatcgac tcctcagggg atgagcagtc cctgctggaa 240  
 cttatcatca ccaccaagaa gcgggaggct cgccagatcc tggaccagac gccggtgaag 300  
 gagctgggtga gcctcaagtga gaagcggtac gggcgggcgt acttctgcat gctgggtgcc 360  
 atatatctgc tgtacatcat ctgcttcacc atgtgctgca tctaccgccc cctcaagccc 420  
 aggaccaata accgcacgag ccccggggac aacaccctct tacagcagaa gctacttcag 480  
 gaagcctaca tgacctctaa ggacgatata cggctggctg gggagctggt gactgtcatt 540  
 ggggctatca tcatcctgct ggtagagggt ccagacatct tcagaatggg ggtcactcgc 600  
 ttctttggac agaccatcct tgggggcccc ttccatgtcc tcatcatcac ctatgccttc 660  
 atggtgctgg tgaccatggt gatgcggctc atcagtgcca gcggggagggt ggtacccatg 720  
 tcctttgcac tcgtgctggg ctggtgcaac gtcagtact tcgcccagag attccagatg 780  
 ctaggccctc tcaccatcat gattcagaag atgattttg gcgacctgat gcgattctgc 840  
 tggctgatgg ctgtggtcat cctgggcttt gcttcagcct tctatatcat cttccagaca 900  
 gaggaccocg aggagctagg ccacttctac gactaccoca tggccctggt cagcaccttc 960  
 gagctgttcc ttaccatcat cgatggcccc gccaaactaca acgtggacct gcccttcatt 1020  
 tacagcatca cctatgctgc ctttgccatc atcgccacac tgctcatgct caacctcctc 1080  
 attgccatga tgggcgacac tcaactggcg gtggcccatg agcgggatga gctgtggagg 1140  
 gccagattg tggccaccac ggtgatgctg gagcggaagc tgccctcgctg cctgtggcct 1200  
 cgctccggga tctgcggaag ggagtatggc ctgggagacc gctgggttcct gcgggtggaa 1260  
 gacaggcaag atctcaaccg gcagcggatc caacgctacg cacaggcctt ccacaccocg 1320  
 ggctctgagg atttggaaca agactcagtg gaaaaactag agctgggctg tcccttcagc 1380

```

ccccacctgt cccttcctat gccctcagtg tctcgaagta cctcccgcag cagtgccaat 1440
tgggaaaggc ttcggcaagg gaccctgagg agagacctgc gtgggataat caacaggggt 1500
ctggaggacg gggagagctg ggaatatcag atctga 1536

```

&lt;210&gt; 765

&lt;211&gt; 1533

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 765

```

atgtacaacc tgttgctgtc ctacgacaga catggggacc acctgcagcc cctggacctc 60
gtgcccattc accagggtct cacccttttc aagctggctg gaggggagg taacctgtg 120
atgtttcagc acctgatgca gaagcggaag cacaccagtg ggaegtatgg accactgacc 180
tcgactctct atgacctcac agagatcgac tcctcagggg atgagcagtc cctgctggaa 240
cttatcatca ccaccaagaa gcgggaggct cgccagatcc tggaccagac gccggtgaag 300
gagctgggtga gcctcaagtg gaagcggtag gggcgggcgt acttctgcat gctgggtgcc 360
atatatctgc tgtacatcat ctgcttcacc atgtgctgca tctaccgccc cctcaagccc 420
aggaccaata accgcacgag ccccggggac aacaccctct tacagcagaa gctacttcag 480
gaagcctaca tgaccctaa ggacgatatc cggctggctg gggagctggt gactgtcatt 540
ggggctatca tcatcctgct ggtagaggtt ccagacatct tcagaatggg ggtcactcgc 600
ttctttggac agaccatcct tgggggcccc tccatgtcc tcatcatcac ctatgccttc 660
atggtgctgg tgaccatggt gatgcggctc atcagtgccg gcggggagggt ggtacccatg 720
tcctttgcac tcgtgctggg ctggtgcaac gtcattgtact tcgcccagggt attccagatg 780
ctaggcccct tcaccatcat gattcagaag atgatttttg gcgacctgat gcgattctgc 840
tggtgatggt ctgtggtcat cctgggcttt gcttcagcct tctatatcat cttccagaca 900
gaggaccccg aggagctagg ccacttctac gactacccca tggccctgtt cagcaccttc 960
gagctgttcc ttaccatcat cgatggccca gccaaactaca acgtggacct gcccttcatt 1020
tacagcatca cctatgctgc ctttgccatc atcgccacac tgctcatgct caacctcctc 1080
attgccatga tgggcgacac tcaactggcg gtggcccatg agcgggatga gctgtggagg 1140
gccagatttg tggccaccac ggtgatgctg gagcggaagc tgccctgctg cctgtggcct 1200
cgctccggga tctgcggacg ggagtatggc ctgggagacc gctggttcct gcgggtggaa 1260
gacaggcaag atctcaaccg gcagcggatc caacgctacg cacaggcctt ccacaccggg 1320
ggctctgagg atttgacaaa agactcagtg gaaaaactag agctgggctg tcccttcagc 1380
ccccacctgt cccttcctat gccctcagtg tctcgaagta cctcccgcag cagtgccaat 1440
tgggaaaggc ttcggcaagg gaccctgagg agagacctgc gtgggataat caacaggggt 1500
ctggaggacg gggagagctg ggaatatcag atc 1533

```

&lt;210&gt; 766

&lt;211&gt; 511

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 766

```

Met Tyr Asn Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln
      5              10              15

Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu
      20              25              30

Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys
      35              40              45

Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr
      50              55              60

Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu
      65              70              75              80

```

Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln  
 85 90 95  
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg  
 100 105 110  
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys  
 115 120 125  
 Phe Thr Met Cys Cys Ile Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn  
 130 135 140  
 Arg Thr Ser Pro Arg Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln  
 145 150 155 160  
 Glu Ala Tyr Met Thr Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu  
 165 170 175  
 Val Thr Val Ile Gly Ala Ile Ile Ile Leu Leu Val Glu Val Pro Asp  
 180 185 190  
 Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln Thr Ile Leu Gly  
 195 200 205  
 Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe Met Val Leu Val  
 210 215 220  
 Thr Met Val Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met  
 225 230 235 240  
 Ser Phe Ala Leu Val Leu Gly Trp Cys Asn Val Met Tyr Phe Ala Arg  
 245 250 255  
 Gly Phe Gln Met Leu Gly Pro Phe Thr Ile Met Ile Gln Lys Met Ile  
 260 265 270  
 Phe Gly Asp Leu Met Arg Phe Cys Trp Leu Met Ala Val Val Ile Leu  
 275 280 285  
 Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe Gln Thr Glu Asp Pro Glu  
 290 295 300  
 Glu Leu Gly His Phe Tyr Asp Tyr Pro Met Ala Leu Phe Ser Thr Phe  
 305 310 315 320  
 Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro Ala Asn Tyr Asn Val Asp  
 325 330 335  
 Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala Ala Phe Ala Ile Ile Ala  
 340 345 350  
 Thr Leu Leu Met Leu Asn Leu Leu Ile Ala Met Met Gly Asp Thr His  
 355 360 365  
 Trp Arg Val Ala His Glu Arg Asp Glu Leu Trp Arg Ala Gln Ile Val  
 370 375 380  
 Ala Thr Thr Val Met Leu Glu Arg Lys Leu Pro Arg Cys Leu Trp Pro

304

385                      390                      395                      400  
 Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly Leu Gly Asp Arg Trp Phe  
                          405                      410                      415  
 Leu Arg Val Glu Asp Arg Gln Asp Leu Asn Arg Gln Arg Ile Gln Arg  
                          420                      425                      430  
 Tyr Ala Gln Ala Phe His Thr Arg Gly Ser Glu Asp Leu Asp Lys Asp  
                          435                      440                      445  
 Ser Val Glu Lys Leu Glu Leu Gly Cys Pro Phe Ser Pro His Leu Ser  
                          450                      455                      460  
 Leu Pro Met Pro Ser Val Ser Arg Ser Thr Ser Arg Ser Ser Ala Asn  
                          465                      470                      475                      480  
 Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg Arg Asp Leu Arg Gly Ile  
                          485                      490                      495  
 Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser Trp Glu Tyr Gln Ile  
                          500                      505                      510

&lt;210&gt; 767

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 767

Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln  
                          5                      10                      15  
 Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu  
                          20                      25                      30  
 Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys  
                          35                      40                      45  
 Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr  
                          50                      55                      60  
 Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu  
                          65                      70                      75                      80  
 Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln  
                          85                      90                      95  
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg  
                          100                      105                      110  
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys  
                          115                      120                      125  
 Phe Thr Met Cys Cys Ile  
                          130

305

<210> 768  
<211> 55  
<212> PRT  
<213> Homo sapiens

<400> 768  
Ala Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn Arg Thr Ser Pro Arg  
                  5                  10                  15  
  
Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln Glu Ala Tyr Met Thr  
                  20                  25                  30  
  
Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu Val Thr Val Ile Gly  
                  35                  40                  45  
  
Ala Ile Ile Ile Leu Leu Val  
                  50                  55

<210> 769  
<211> 39  
<212> PRT  
<213> Homo sapiens

<400> 769  
Glu Val Pro Asp Ile Phe Arg Met Gly Val Thr Arg Phe Phe Gly Gln  
                  5                  10                  15  
  
Thr Ile Leu Gly Gly Pro Phe His Val Leu Ile Ile Thr Tyr Ala Phe  
                  20                  25                  30  
  
Met Val Leu Val Thr Met Val  
                  35

<210> 770  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 770  
Met Arg Leu Ile Ser Ala Ser Gly Glu Val Val Pro Met Ser Phe Ala  
                  5                  10                  15  
  
Leu Val Leu

<210> 771  
<211> 52  
<212> PRT  
<213> Homo sapiens

<400> 771  
Gly Trp Cys Asn Val Met Tyr Phe Ala Arg Gly Phe Gln Met Leu Gly  
                  5                  10                  15  
  
Pro Phe Thr Ile Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg



306

20 25 30  
 Phe Cys Trp Leu Met Ala Val Val Ile Leu Gly Phe Ala Ser Ala Phe  
 35 40 45  
 Tyr Ile Ile Phe  
 50  
  
 <210> 772  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 772  
 Gln Thr Glu Asp Pro Glu Glu Leu Gly His Phe Tyr Asp Tyr Pro Met  
 5 10 15  
 Ala Leu Phe Ser Thr Phe Glu Leu Phe Leu Thr Ile Ile Asp Gly Pro  
 20 25 30  
 Ala Asn Tyr Asn Val Asp Leu Pro Phe Met Tyr Ser Ile Thr Tyr Ala  
 35 40 45  
 Ala Phe Ala Ile Ile Ala Thr Leu Leu Met Leu Asn Leu Leu Ile Ala  
 50 55 60  
 Met Met Gly Asp Thr His Trp Arg Val Ala His Glu Arg Asp Glu Leu  
 65 70 75 80  
 Trp Arg Ala Gln Ile Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu  
 85 90 95  
 Pro Arg Cys Leu Trp Pro Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly  
 100 105 110  
 Leu Gly Asp Arg Trp Phe Leu Arg Val Glu Asp Arg Gln Asp Leu Asn  
 115 120 125  
 Arg Gln Arg Ile Gln Arg Tyr Ala Gln Ala Phe His Thr Arg Gly Ser  
 130 135 140  
 Glu Asp Leu Asp Lys Asp Ser Val Glu Lys Leu Glu Leu Gly Cys Pro  
 145 150 155 160  
 Phe Ser Pro His Leu Ser Leu Pro Met Pro Ser Val Ser Arg Ser Thr  
 165 170 175  
 Ser Arg Ser Ser Ala Asn Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg  
 180 185 190  
 Arg Asp Leu Arg Gly Ile Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser  
 195 200 205  
 Trp Glu Tyr Gln Ile  
 210

<210> 773  
 <211> 1302  
 <212> DNA  
 <213> Homo sapiens

<400> 773  
 tggacaaagg gggcacaca ttcttccat acggttgagc ctctacctgc ctggtgctgg 60  
 tcacagttca gcttcttcat gatgggtggat cccaatggca atgaatccag tgctacatac 120  
 ttcatcctaa taggcctccc tggtttagaa gaggctcagt tctggttggc cttcccattg 180  
 tgctccctct acctattgc tgtgctaggt aacttgacaa tcatctacat tgtgcggact 240  
 gagcacagcc tgcattgagcc catgtatata tttctttgca tgccttcagg cattgacatc 300  
 ctcatctcca cctcatccat gcccaaatg ctggccatct tctggttcaa ttccactacc 360  
 atccagtttg atgcttgtct gctacagatg tttgccatcc actccttacc tggcatggaa 420  
 tccacagtgc tgcctggccat ggcttttgac cgctatgtgg ccatctgtca cccactgcgc 480  
 catgccacag tacttacgtt gcctcgtgtc accaaaattg gtgtggctgc tgtggtgcgg 540  
 ggggctgcac tgatggcacc ccttcctgtc ttcatcaagc agctgccctt ctgccgctcc 600  
 aatatccttt cccattccta ctgcctacac caagatgtca tgaagctggc ctgtgatgat 660  
 atccgggtca atgtcgtcta tggccttacc gtcacatct cggccattgg cctggactca 720  
 cttctcatct cttctcata tctgcttatt ctttaagactg tgttgggctt gacacgtgaa 780  
 gccaggcca aggcatttgg cacttgctgc tctcatgtgt gtgctgtgtt catattctat 840  
 gtacctttca ttggattgtc catggtgcat cgcttttagca agcggcgtga ctctccgctg 900  
 cccgtcatct tggccaatat ctatctgctg gttcctcctg tgcacaacc aattgtctat 960  
 ggagtgaaga caaaggagat tcgacagcgc atccttcgac tttccatgt ggccacacac 1020  
 gcttcagagc cctaggtgtc agtgatcaaa ctctctttcc attcagagtc ctctgattca 1080  
 gattttaagt ttaacatttt ggaagacagt attcagaaaa aaaatttcct taataaaaaat 1140  
 acaactcaga tccttcaaat atgaaactgg ttggggaatc tccatttttt caatattatt 1200  
 ttcttctttg ttttcttgct acatataatt attaataccc tgactaggtt gtggtttgag 1260  
 ggttattact tttcatttta ccatgcagtc caaatctaaa ct 1302

<210> 774  
 <211> 2061  
 <212> DNA  
 <213> Homo sapiens

<400> 774  
 acgattcgac agcgcattct tcgacttttc catgtggcca cacacgcttc agagccctag 60  
 gtgtcagtga tcaaacttct tttccattca gattcctctg attcagattt taatgttaac 120  
 attttgaag acagtattca gaaaaaaat ttccttaata aaaatacaac tcagatcctt 180  
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&lt;211&gt; 957

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 775

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&lt;211&gt; 954

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 776

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310

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&lt;210&gt; 778

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 778

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&lt;210&gt; 779

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 779

Arg Thr Glu His Ser Leu His Glu Pro  
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&lt;210&gt; 780

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 780

Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln Phe Asp  
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&lt;210&gt; 781

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 781

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 <213> Homo sapiens

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&lt;210&gt; 789

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 789

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      35      40      45
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      50      55      60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
      65      70      75      80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
      85      90      95
Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
      100      105      110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
      115      120      125
Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
      130      135      140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val
      145      150      155      160
Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
      165      170      175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
      180      185      190
Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
      195      200      205
Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
      210      215      220
Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
      225      230      235      240
Cys Ile Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
      245      250      255
Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
      260      265      270
Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
      275      280      285
Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
      290      295      300
Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
      305      310      315      320
Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn
      325      330      335
Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
      340      345      350

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[illegible]

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<400> 791
Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys Cys Ser Asn
      5                      10                      15
Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn Pro Ser Asn
      20                      25                      30
Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp Glu Asn Arg
      35                      40                      45
Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val Tyr Ser Ser
      50                      55                      60
Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp Asn Glu Asn
      65                      70                      75                      80

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Tyr	Gly	Arg	Ala	Ala	Cys	Arg	Asp	Met	Gly	Tyr	Lys	Asn	Asn	Phe	Tyr
Ser	Ser	Gln	Gly	Ile	Val	Asp	Asp	Ser	Gly	Ser	Thr	Ser	Phe	Met	Lys
Leu	Asn	Thr	Ser	Ala	Gly	Asn	Val	Asp	Ile	Tyr	Lys	Lys	Leu	Tyr	His
Ser	Asp	Ala	Cys	Ser	Ser	Lys	Ala	Val	Val	Ser	Leu	Arg	Cys	Ile	Ala
Cys	Gly	Val	Asn	Leu	Asn	Ser	Ser	Arg	Gln	Ser	Arg	Ile	Val	Gly	Gly
Glu	Ser	Ala	Leu	Pro	Gly	Ala	Trp	Pro	Trp	Gln	Val	Ser	Leu	His	Val
Gln	Asn	Val	His	Val	Cys	Gly	Gly	Ser	Ile	Ile	Thr	Pro	Glu	Trp	Ile
Val	Thr	Ala	Ala	His	Cys	Val	Glu	Lys	Pro	Leu	Asn	Asn	Pro	Trp	His
Trp	Thr	Ala	Phe	Ala	Gly	Ile	Leu	Arg	Gln	Ser	Phe	Met	Phe	Tyr	Gly
Ala	Gly	Tyr	Gln	Val	Glu	Lys	Val	Ile	Ser	His	Pro	Asn	Tyr	Asp	Ser
Lys	Thr	Lys	Asn	Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln	Lys	Pro	Leu
Thr	Phe	Asn	Asp	Leu	Val	Lys	Pro	Val	Cys	Leu	Pro	Asn	Pro	Gly	Met
Met	Leu	Gln	Pro	Glu	Gln	Leu	Cys	Trp	Ile	Ser	Gly	Trp	Gly	Ala	Thr
Glu	Glu	Lys	Gly	Lys	Thr	Ser	Glu	Val	Leu	Asn	Ala	Ala	Lys	Val	Leu
Leu	Ile	Glu	Thr	Gln	Arg	Cys	Asn	Ser	Arg	Tyr	Val	Tyr	Asp	Asn	Leu
Ile	Thr	Pro	Ala	Met	Ile	Cys	Ala	Gly	Phe	Leu	Gln	Gly	Asn	Val	Asp
Ser	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Val	Thr	Ser	Lys	Asn	Asn
Ile	Trp	Trp	Leu	Ile	Gly	Asp	Thr	Ser	Trp	Gly	Ser	Gly	Cys	Ala	Lys
Ala	Tyr	Arg	Pro	Gly	Val	Tyr	Gly	Asn	Val	Met	Val	Phe	Thr	Asp	Trp
Ile	Tyr	Arg	Gln	Met	Arg	Ala	Asp	Gly							

<210> 792

**<211> 595**

<21.2> PRT

<213> Homo sapiens

<400> 792

Met	Ser	Phe	Leu	Asn	Phe	Thr	Ala	Val	Leu	Phe	Ala	Ala	Ser	Ser	Ala
1				5					10					15	
Leu	Ala	Ala	Pro	Val	Asn	Thr	Thr	Thr	Glu	Asp	Glu	Thr	Ala	Gln	Ile
			20					25					30		
Pro	Ala	Glu	Ala	Val	Ile	Gly	Tyr	Ser	Asp	Leu	Glu	Gly	Asp	Phe	Asp
		35				40					45				
Val	Ala	Val	Leu	Pro	Phe	Ser	Asn	Ser	Thr	Asn	Asn	Gly	Leu	Leu	Phe
	50				55					60					
Ile	Asn	Thr	Thr	Ile	Ala	Ser	Ile	Ala	Ala	Lys	Glu	Glu	Gly	Val	Ser
65				70						75				80	

Leu Glu Lys Arg Glu Ala Glu Ala Met Val Leu Gly Ile Gly Pro Val  
 85 90 95  
 Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp  
 100 105 110  
 Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu  
 115 120 125  
 Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala  
 130 135 140  
 Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile  
 145 150 155 160  
 Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro  
 165 170 175  
 Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg  
 180 185 190  
 Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu  
 195 200 205  
 Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro  
 210 215 220  
 Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile  
 225 230 235 240  
 Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala  
 245 250 255  
 Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser  
 260 265 270  
 Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly  
 275 280 285  
 Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr  
 290 295 300  
 Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met  
 305 310 315 320  
 Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln  
 325 330 335  
 Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp  
 340 345 350  
 Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile  
 355 360 365  
 Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly  
 370 375 380  
 Thr Arg Ala Val Tyr Leu Ala Ser Val Ala Phe Pro Val Ala Ala  
 385 390 395 400  
 Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Thr Ala Ser Ala  
 405 410 415  
 Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr  
 420 425 430  
 Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr  
 435 440 445  
 Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser  
 450 455 460  
 Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val  
 465 470 475 480  
 Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly  
 485 490 495  
 Ala Ser Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr  
 500 505 510  
 Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile  
 515 520 525  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 530 535 540

[illegible]